

National Institute of Allergy and Infectious Diseases

PROFILE

Fiscal Year 2004



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES



NATIONAL INSTITUTES OF HEALTH



NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

Front cover photo: Scientist prepares a monolayer of Vero cells infected with the virus that causes dengue fever in humans.

National Institute of Allergy and Infectious Diseases

PROFILE

Fiscal Year 2004



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

National Institute of Allergy and Infectious Diseases

National Institute of Allergy and Infectious Diseases



This is a stylized representation of an antibody, a protein made by the body's immune system cells to protect it against invading foreign substances.

INTRODUCTION

The National Institute of Allergy and Infectious Diseases (NIAID) conducts and supports basic and applied research to better understand, treat, and ultimately prevent infectious, immunologic, and allergic diseases. For more than 50 years, NIAID research has led to new therapies, vaccines, diagnostic tests, and other technologies that have improved the health of millions of people in the United States and around the world. The scope of the NIAID research portfolio has expanded considerably in recent years in response to new challenges such as bioterrorism; emerging and re-emerging infectious diseases, including acquired immunodeficiency syndrome (AIDS), influenza, severe acute respiratory syndrome (SARS), West Nile virus, malaria, and tuberculosis; and the increase in asthma prevalence among children in this country. The growth of NIAID programs also has been driven by unprecedented scientific opportunities in the core NIAID scientific disciplines of microbiology, immunology, and infectious diseases. Advances in these key fields have led to a better understanding of the human immune system and the mechanisms of infectious and immune-mediated diseases.

The threat of bioterrorism has created new challenges for medicine and public health. Our Nation's ability to detect and respond to acts of bioterror requires new and improved countermeasures, including diagnostics, vaccines, and therapies. The development of countermeasures is driven by biomedical research on dangerous, disease-causing microbes and on the immune system response to these pathogens. The National Institutes of Health (NIH) and NIAID support much of this research. As the lead agency at NIH for infectious diseases and immunology research, NIAID has set research priorities and goals for each microorganism or toxin that might be used as an agent of bioterrorism, with particular emphasis on "Category A" agents—those considered to be

the worst bioterror threats. NIAID's biodefense program includes both short- and long-term research targeted at the design, development, and evaluation of the specific public health tools or countermeasures needed to control a bioterrorist-caused outbreak. NIAID's advances in biodefense research are discussed in the *NIAID Biodefense Research Agenda for CDC Category A Agents Progress Report* and the *NIAID Biodefense Research Agenda for Category B and C Priority Pathogens Progress Report*.

We anticipate that the large investment in research on biodefense will provide new insights relevant to other diseases. NIAID research on microbial biology and on the pathogenesis of organisms with bioterror potential will lead to a better understanding of other more common and naturally occurring infectious diseases that afflict people here and abroad. In particular, the advancement of knowledge should have an enormous positive impact on our ability to diagnose, treat, and prevent major infectious killers, such as malaria, tuberculosis, human immunodeficiency virus (HIV)/AIDS, and a spectrum of emerging and re-emerging diseases, such as West Nile virus, dengue, influenza, and multidrug-resistant microbes. Furthermore, and importantly, the NIAID biodefense research agenda promises to enhance our understanding of the molecular and cellular mechanisms of innate immunity and its relationship to adaptive immunity. Such knowledge will help in the search for new ways to treat and prevent a variety of immune-mediated diseases, such as systemic lupus erythematosus, type 1 diabetes, and rheumatoid arthritis. New insights into the mechanisms of regulation of the human immune system also will have positive spinoffs for diseases such as cancer, immune-mediated neurological diseases, and allergic and hypersensitivity diseases, as well as for the prevention of rejection of transplanted organs, cells, and tissues.

Vaccine research has long been a cornerstone of NIAID research. Effective vaccines have

contributed enormously to improvements in public health worldwide, and research supported by NIAID has led to new or improved vaccines for a variety of serious diseases, including rabies, meningitis, whooping cough, hepatitis A and B, chickenpox, and pneumococcal pneumonia. NIAID has three broad goals in vaccine research: identifying new vaccine candidates to prevent diseases for which no vaccines currently exist, improving the safety and efficacy of existing vaccines, and designing novel vaccine approaches such as new vectors and adjuvants.

One of the important challenges for the 21st century is the development of safe and effective vaccines for the three greatest microbial killers worldwide: HIV/AIDS, malaria, and tuberculosis. These three diseases account for one-third to one-half of healthy years lost in less-developed countries. NIAID has a robust portfolio of vaccine research and development for these and other diseases of global importance, including those caused by agents of bioterrorism. Another important focus is the development of next-generation influenza vaccines made with modern technologies that improve on the current egg-based method of production. Significant progress has been made in developing new vaccine candidates against both “interpandemic” flu strains that currently are circulating among humans, as well as strains with pandemic potential, such the H5N1 avian influenza seen in humans in Southeast Asia.

Despite recent progress in treatment and prevention, HIV disease and AIDS continue to exact an enormous toll throughout the world. Estimates on the scope of the HIV/AIDS pandemic are profoundly sobering. An estimated 39 million people worldwide are living with HIV/AIDS, and approximately 11 of every 1,000 adults aged 15 to 49 are HIV-infected. In 2004 alone, HIV/AIDS-associated illnesses caused the deaths of approximately 3.1 million people worldwide. More than 95 percent of these infections and deaths have occurred in developing

countries, most of which also are burdened by other significant health challenges.¹ To help turn the tide of the global HIV/AIDS pandemic, NIAID has established research collaborations with international colleagues in more than 50 countries to develop comprehensive approaches to the HIV pandemic, encompassing vaccine development and other prevention activities, therapeutics, and care of the HIV-infected person. These collaborations already have yielded important results, notably in developing methods to reduce mother-to-child transmission of HIV.

NIAID-sponsored researchers have made critical discoveries about the basic biology of HIV and the immune response to HIV infection, which in turn have led to the development of therapies that suppress the growth of the virus in the body. Although much has been learned in recent years, questions remain about the molecular interactions involved in the regulation of HIV expression and replication, why the host immune response fails to control the infection, and how reservoirs of virus persist in the body despite highly active antiretroviral treatment (HAART). NIAID continues to search for more scientific information about how the virus attacks the body and how the body defends itself, both of which are critical for identifying additional targets for therapeutic interventions and vaccines.

An important NIAID research focus is the immune system, the complex network of cells, tissues, and organs that work together to defend the body against attacks by foreign invaders such as bacteria, viruses, parasites, and fungi. Because the human body provides an ideal environment for many microbes, they try to break in. It is the immune system's job to keep them out or, failing that, to seek out and destroy them. When the immune system hits the wrong target or is crippled, however, many diseases may result, including asthma and allergy diseases, arthritis, or AIDS. NIAID-funded research in basic and clinical immunology has led to many promising approaches for treating individuals

with immunologic conditions such as multiple sclerosis, type 1 diabetes, and asthma. For example, researchers are developing novel ways to selectively block inappropriate or destructive immune responses while leaving protective immune responses intact, an area of research known as tolerance induction. The NIAID-supported Immune Tolerance Network (ITN) is an international consortium of approximately 80 basic and clinical scientists and physicians at more than 40 institutions in the United States, Canada, Europe, and Australia. ITN has 18 approved clinical protocols that are enrolling patients, or will do so soon, in areas such as islet transplantation for type 1 diabetes, kidney transplantation, autoimmune diseases, and asthma and allergic diseases. In September 2004, NIAID launched a three-site consortium that will work to improve the outcomes of organ transplantation. The percentage of patients who live for a year after an organ transplant has risen dramatically over the past 15 years, but there has been only modest success in improving the odds of long-term survival. This research consortium will move us closer to minimizing the debilitating and sometimes fatal complications of organ transplantation.²

For the past decade, NIAID also has focused on reducing the significant and growing burden of asthma among inner-city minority children. NIAID's Inner-City Asthma Study has investigated novel interventions to improve the health of inner-city children with asthma. One approach, called a physician feedback intervention, involves periodic reports to the child's doctor about the status of the child's asthma. These reports, generated from bimonthly phone interviews with parents, recommend changes in the child's treatment regimen

according to National Heart, Lung, and Blood Institute guidelines, if warranted. Another method involves an environmental intervention to identify and remove asthma triggers, such as cigarette smoke or cockroaches, from the child's home. Both interventions are reducing healthcare utilization, and the children receiving the environmental intervention gained an additional 3 weeks of symptom-free days during the intervention year. We are working to make such interventions available nationwide.

Profile describes the Institute's activities in areas of basic research and clinical investigation and provides overviews of the major accomplishments and goals of the various scientific programs within the Institute. *Profile* also includes information on the organization and staff of NIAID, the Institute's budget, and its extramural grants, contracts, and research training programs.

We still have much to discover about many infectious and immune-mediated diseases and how best to diagnose, treat, and prevent them. However, with a strong research base, talented investigators in the United States and abroad, and the availability of powerful new research tools, we fully expect that our basic and applied research programs will provide the essential elements to enhance our defenses against those who would attempt to harm us with bioterrorism, to develop new tools in the fights against HIV/AIDS and other infectious diseases, and to improve therapies and management of immune-mediated diseases.

Anthony S. Fauci, M.D.

Director

National Institute of Allergy and Infectious Diseases

¹ UNAIDS. AIDS epidemic update: 2004. Available at <http://www.unaids.org/wad2004/report.html>.

² NIAID Forms Clinical Consortium to Improve Success of Organ Transplants. *NIH News*, Sept. 13, 2004. Available at: www.niaid.nih.gov/Newsroom/Releases/organtrans.html.

IN MEMORY OF JOHN R. LA MONTAGNE, PH.D., FORMER NIAID DEPUTY DIRECTOR

John R. La Montagne, Ph.D., Deputy Director of the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH), died suddenly in Mexico City on November 2, 2004. He was 61.



“All of us are profoundly saddened by the loss of John La Montagne,” said NIAID Director Anthony S. Fauci, M.D. “Personally, he was a dear friend and one of the finest people I have ever known. Professionally, in an NIH career spanning nearly 30 years, his leadership and commitment to improving global health were remarkable. His generosity, wit, even-handedness, and kindness made him a friend to all who knew him. He will be sorely missed.”

Dr. La Montagne, a native of Mexico City, Mexico, received his Ph.D. from Tulane University in 1971. In 1976, he came to NIH as the Influenza Program Officer at NIAID. He became the Program Officer for the Viral Vaccines Program in 1983, and the Influenza and Viral Respiratory Diseases Program Officer in 1984. Beginning in 1986, Dr. La Montagne assumed the role of Director of the AIDS Program. In 1987, he was appointed Director of the Microbiology and Infectious Diseases Program, which became a Division in 1988. Dr. La Montagne was appointed Deputy Director of NIAID in February 1998.

Dr. La Montagne made significant contributions to the national and international effort against emerging and re-emerging infectious diseases, including biodefense-related activities, and has been recognized internationally for his leadership in this area. He played a central role in the organization of the Multilateral Initiative on Malaria, an international effort involving research, control, and development agencies

from the U.S., Europe, and Africa. In addition, he served as a member of the Scientific Advisory Groups of Experts on Vaccines and Biologicals as well as for Vaccines and Immunization for the World Health Organization (WHO). He chaired the WHO Task Force on Strategic Planning for the Children’s Vaccine Initiative, advised the Pan

American Health Organization on its programs in vaccine research implementation, and served as a member of the board of the Global Alliance for TB Drug Development. Dr. La Montagne also served as a member of the Biomedical Research Confederation Executive Steering Committee at Fort Detrick, Maryland, and as cochair of the Research and Development Gaps Working Group, a component of the Weapons of Mass Destruction Subcommittee of the National Science and Technology Council. His outstanding administrative leadership at NIH included membership on the NIH Community Advisory Board for Security and the recently formed NIH Ethics Advisory Committee.

As an influential contributor to the field of infectious diseases, Dr. La Montagne delivered numerous major lectures all over the world. He received many prestigious awards for his scientific accomplishments, including the Public Health Service Special Recognition Award for leadership in childhood vaccine research programs, the Surgeon General’s Certificate of Appreciation, the Presidential Meritorious Executive Rank Award, the Distinguished Executive Award for his work in the areas of infectious diseases research of global health relevance, the Secretary’s Award for Distinguished Service for leadership of acellular pertussis vaccine trials, and most recently the Secretary’s Award for Distinguished Service for design and implementation of critically important biodefense strategies.

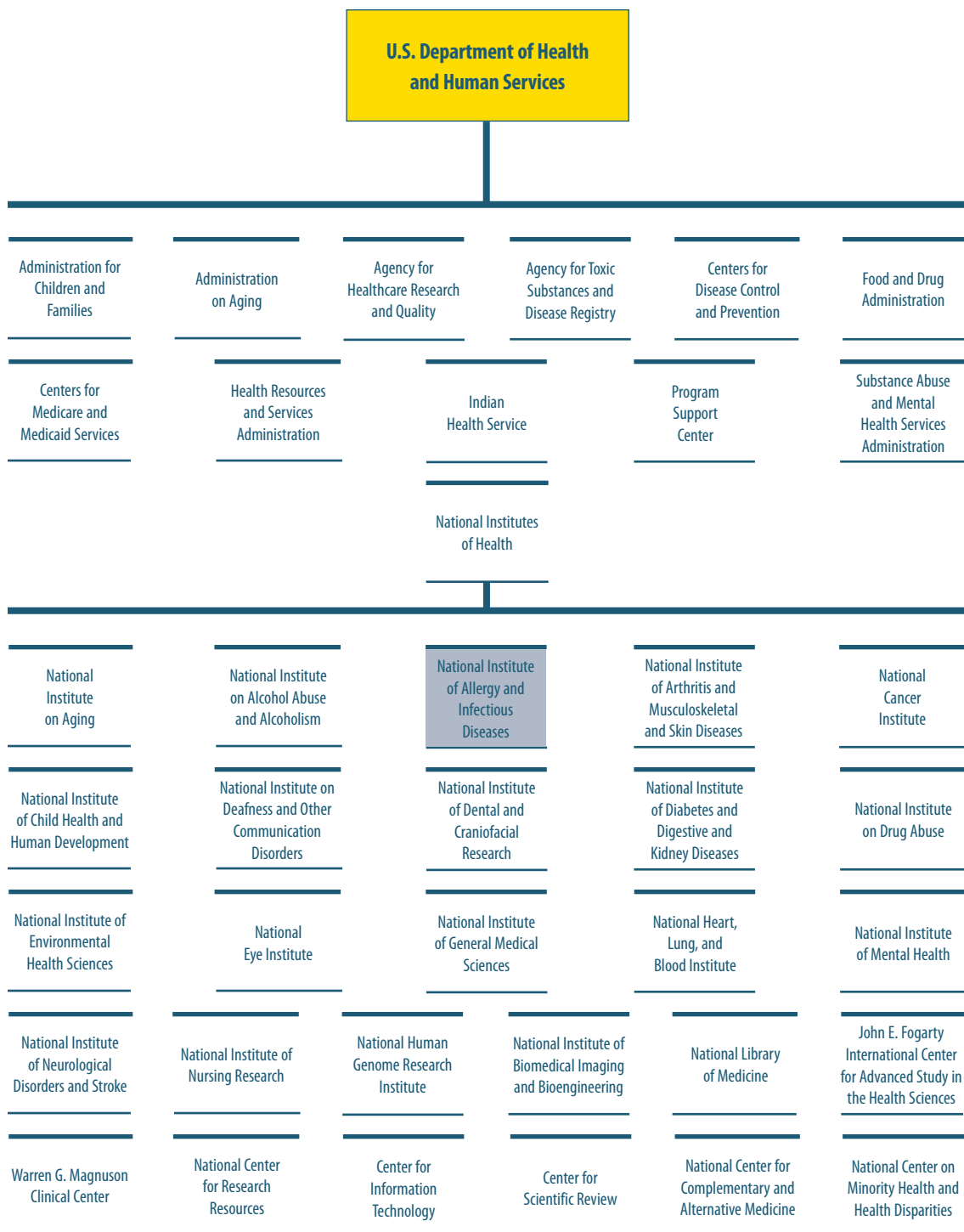
TABLE OF CONTENTS

Introduction	i
In Memory of Dr. La Montagne	v
Organizational Structure	1
Location of NIAID in the U.S. Department of Health and Human Services	1
NIAID Organizational Chart	2
Organizational Overviews	3
Office of the Director	3
Outreach Activities.....	5
Research Planning.....	8
Division of Acquired Immunodeficiency Syndrome	11
Division of Allergy, Immunology, and Transplantation	17
Division of Microbiology and Infectious Diseases	21
Division of Intramural Research.....	26
Dale and Betty Bumpers Vaccine Research Center	30
Division of Extramural Activities	37
Selected Scientific Areas of Research	39
Acquired Immunodeficiency Syndrome (AIDS).....	39
Antimicrobial Resistance.....	45
Asthma and Allergic Diseases	49
Autoimmune Diseases.....	52
Biodefense	54
Bioengineering, Bioinformatics, and Advanced Technologies	61
Drug Research and Development	64
Emerging and Re-emerging Infectious Diseases.....	71
List of Emerging and Re-emerging Diseases 2004.....	73
Genomics	83
Global Health.....	90
Hepatitis C.....	94
Immune Tolerance.....	97
Malaria	100
Minority and Women's Health.....	103
Sexually Transmitted Infections	114

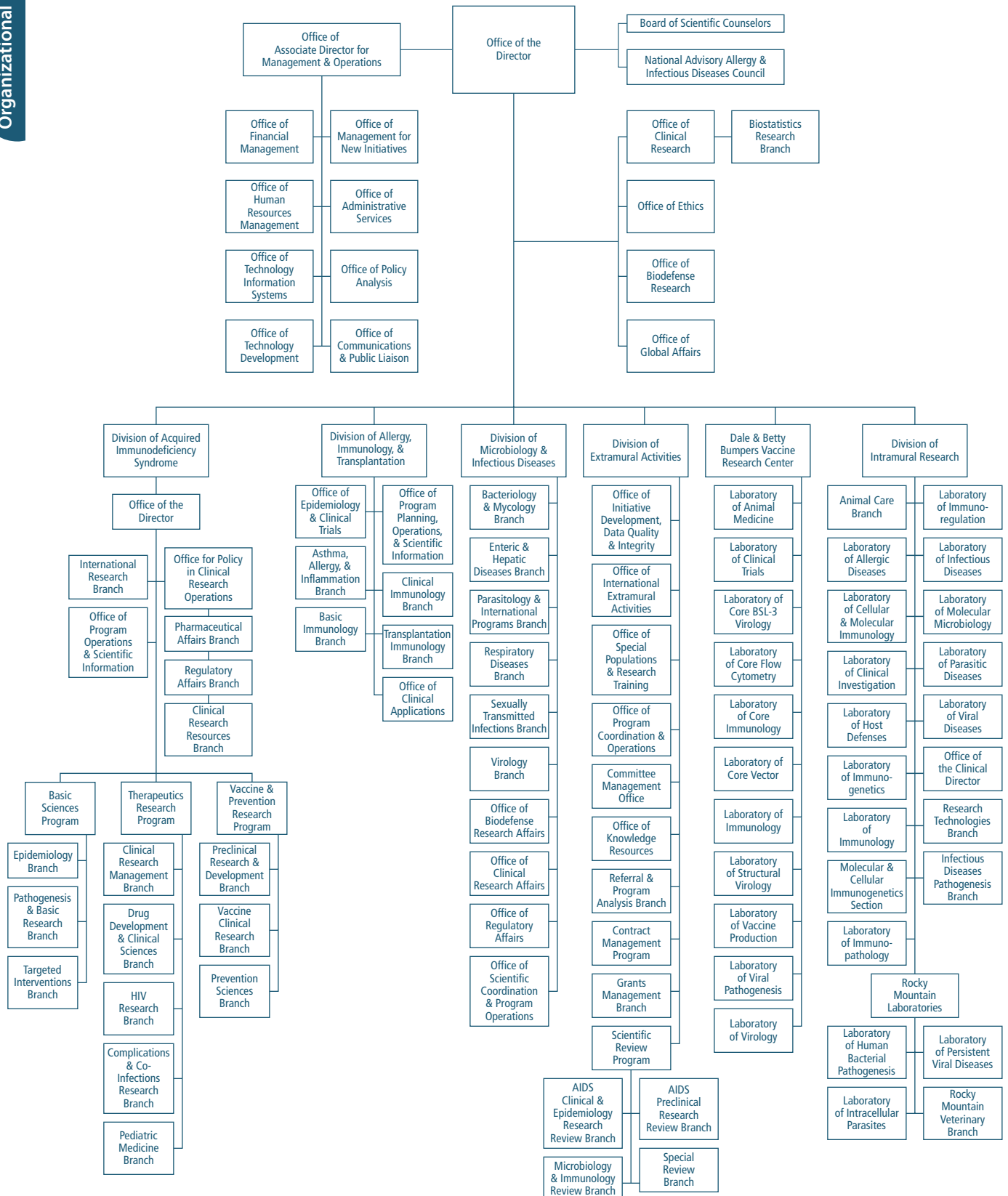
Transplantation	118
Tuberculosis.....	121
Vaccine Research and Development.....	126
NIAID-Supported Repositories.....	136
References	141
Council, Review Committees, and Working Group	145
National Advisory Allergy and Infectious Diseases Council.....	145
Acquired Immunodeficiency Syndrome Research Review Committee	148
AIDS Research Advisory Committee	150
AIDS Vaccine Research Working Group.....	152
Allergy, Immunology, and Transplantation Research Committee	154
Microbiology and Infectious Diseases Research Committee.....	156
Board of Scientific Counselors	158
NIAID Executive Committee.....	160
Budget Overview and Historical Trends	163
Federal Budget Process.....	163
NIH Appropriations History: FY 1993–2004.....	164
NIAID Appropriations History: FY 1993–2004	165
NIAID Funding by Budget Mechanism: FY 2003–2004	166
NIAID Funding by the FY 2004 NIH Plan for HIV-Related Research	167
NIAID Research Training and Career Awards: FY 1994–2004.....	168
Appendices	169
Legislative Chronology	170
Technology Transfer.....	172
NIH Extramural Funding Mechanisms Used by Niaid	177
Acronyms	182
Index	191
General Information.....	201
Directory of NIAID Personnel	201
Location of Buildings Occupied by NIAID Personnel	207

ORGANIZATIONAL STRUCTURE

LOCATION OF NIAID IN THE U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES



NIAID ORGANIZATIONAL CHART



ORGANIZATIONAL OVERVIEWS

OFFICE OF THE DIRECTOR

The Office of the Director (OD), NIAID, provides policy guidance, program development and evaluation, and overall operational and administrative coordination for the Institute. OD is the focal point of relationships with the Director of the NIH as well as with other components of the Department of Health and Human Services (DHHS), other Federal agencies, Congress, professional societies, voluntary health organizations, and other public groups. The activities of OD also include advising and guiding NIAID's key leaders on the principles, practices, laws, regulations, and policies of the Federal equal employment, affirmative action, civil rights, and minority programs. Offices within OD provide critical management and administrative support to the Institute. By carrying out their individual tasks, OD offices play a key role in helping the Institute achieve its mission. Brief descriptions of OD offices follow.

The Office of Administrative Services (OAS) assists NIAID staff members in carrying out their responsibilities by providing administrative and acquisition management support services. These services include procurement, space management, and travel. OAS also develops internal controls in areas such as property accountability and financial monitoring, and coordinates and analyzes organizational changes.

The Office of Clinical Research manages and coordinates the NIAID research programs conducted at the Warren Grant Magnuson Clinical Center located on the NIH Bethesda campus. The Office promotes interactions and collaborations between intramural and extramural investigators and oversees NIAID's Institutional Review Board to provide initial and continuing review of intramural clinical research protocols to protect the welfare of human subjects recruited to participate in biomedical or behavioral research. The Office also provides relevant information from NIAID's intramural clinical research

programs to the NIH community and other Government agencies, as well as to public and private organizations.

The Office of Communications and Public Liaison (OCPL) enables NIAID to meet an important part of its mission by conveying the goals and results of its research programs to health professionals, the news media, and the public. In addition to responding to more than 10,000 requests for information annually, the Office plans educational and media campaigns; develops and disseminates brochures, fact sheets, news releases, and audiovisual products; and produces educational exhibits for national and regional meetings. OCPL also coordinates NIAID's Web site activities.

The Office of Equal Employment Opportunity is responsible for planning, implementing, evaluating, and monitoring programs and initiatives to increase the number of minorities, women, and persons with disabilities in all scientific and administrative areas of the Institute. The Office also develops initiatives that further enhance biomedical research programs at historically black colleges and universities and at Hispanic-serving institutions, and coordinates all activities to implement NIH minority-assistance programs and objectives relevant to the mission of NIAID.

The Office of Ethics provides advice regarding conflict of interest of individuals involved in the conduct of biomedical research, including Government employees, advisory committee members, and non-government employees such as peer reviewers and Data Safety Monitoring Board members. The Office also administers a comprehensive NIAID ethics program that reflects statutory responsibilities and integrity in service to the public.

The Office of Financial Management provides overall financial planning, management, and budget analysis to the Institute Director and all NIAID components and provides budget-related

materials for the NIAID Director's briefings with DHHS, the NIH Director, the Office of Management and Budget, and Congress.

The Office of Global Affairs (OGA) provides overall coordination of NIAID international activities through a matrix of international liaisons; it accomplishes its work with other NIH components and DHHS agencies through the Fogarty International Center. OGA also meets and greets international visitors and delegations, coordinates NIAID participation in bilateral and multilateral programs, negotiates and provides administrative support for the long-term assignment of NIAID staff and representatives overseas, and supervises the OGA/NIAID Epidemiology Group in support of intramural and extramural international projects.

The Human Resources Operations Branch C (NIAID), Division of Human Resources Operations, Office of Human Resources, NIH, provides human resource services for the Institute management, employees, and applicants. These services encompass recruitment and staffing, position management and classification, pay and compensation, employee relations, employee benefits, employee development, and advisory services.

The Office of Management for New Initiatives (OMNI) is responsible for managing the establishment of key resources for new NIAID scientific and administrative initiatives. OMNI also is charged with acquiring and developing physical, human, and contractual infrastructure to fulfill new and expanded NIAID mission requirements.

The Office of Policy Analysis provides support and serves as liaison to program managers to coordinate, integrate, and articulate long-range program goals and strategies; develop and coordinate the Institute's annual planning and reporting process; advise on material for all stages related to congressional budget presentations; direct and coordinate the legislative liaison, tracking, and analysis for the Institute; manage

the Executive Secretariat function; direct and coordinate Freedom of Information Act activities; provide the secretariat function for selected advisory groups, such as the NIAID Executive Committee; prepare the NIAID Director for meetings with various constituency groups; and brief the NIAID Director in preparation for trans-NIH policy meetings.

The Office of Technology Development (OTD) supports NIAID's intramural and extramural research programs by facilitating collaborations between NIAID researchers and external research and development organizations. OTD's staff uses scientific, legal, and business expertise to negotiate agreements with universities, small biotechnology companies, large national and multinational pharmaceutical concerns, and other government institutions. OTD manages NIAID's portfolio of patents and inventions and serves as NIAID's resource for all issues concerning intellectual property. OTD also manages the receipt of Cooperative Research and Development Agreement funds, supports the NIH's licensing program, and tracks license royalty receipts. In addition, OTD provides NIAID investigators with training on NIH technology transfer policies and regulations and guidance on conflict-of-interest issues.

The Office of Technology Information Systems (OTIS) manages technologies supporting NIAID biomedical research programs. The Office provides technology management and development; engineering for scientific, information, and administrative applications; bioinformatics support and coordination; and specialized professional development activities. OTIS works with intramural, extramural, and administrative staff within NIAID and with collaborative programs of the Institute. Activities include policy and technological support, liaison and coordination, and consultation. Program initiatives and projects ensure effective management and broadened and intensified use of technologies to serve NIAID strategic biomedical goals, nationally and worldwide.

OUTREACH ACTIVITIES

The NIAID Office of Communications and Public Liaison (OCPL) is the focal point within the Institute for disseminating research results to the media, health professionals, and the public. An important part of NIAID's mission, this activity includes producing and disseminating print, audiovisual, and Web-based materials; distributing materials at professional and community meetings; and sponsoring workshops and conferences for community healthcare providers and the general public. Other NIAID divisions and offices also initiate and participate in targeted outreach activities.

OCPL produces materials on topics ranging from allergic and immunologic diseases, to AIDS and other sexually transmitted infections, to potential illnesses caused by agents of bioterrorism. These materials include press releases, information sheets, and booklets, which are distributed to more than 10,000 people who contact the Institute from around the world each year. In addition, hundreds of thousands more download or request materials from the NIAID Web site (www.niaid.nih.gov), which is now visited approximately 800,000 times each month.

The NIAID Web site is a searchable site containing a wealth of information about NIAID's organization and research programs, as well as descriptions of NIAID's laboratories. The Extramural Information Center includes program announcements, contact information for key personnel, and many other items of interest to current and potential grantees and contractors.

OCPL has updated and printed its award-winning booklet on allergy—*Airborne Allergens: Something in the Air*—and published a new booklet called *Food Allergy: An Overview*. In addition, OCPL has updated and printed three very popular booklets: *Lyme Disease: The Facts, the Challenges; Understanding Vaccines: What They Are, How They Work*; and *Understanding the*

Immune System: How It Works. OCPL distributed thousands of copies of the previous editions of these booklets to lay public, healthcare providers, research institutions, and researchers around the world. All publications are also available on the NIAID Web site.

Exhibiting at scientific and health-related meetings is a key element of OCPL's outreach efforts. Institute staff distribute materials and answer questions about NIAID research and job opportunities at conferences, including those sponsored by the American Academy of Allergy, Asthma and Immunology; the American Society for Microbiology; the Infectious Diseases Society of America; the Hispanic Association of Colleges and Universities; the American Public Health Association; and the Congressional Black Caucus.

An OCPL communications initiative continues to expand NIAID's efforts to keep hundreds of voluntary and scientific organizations updated about Institute activities. Periodic e-mails provide timely news on NIAID research advances that relate to the specific research interests of the organizations. In addition, OCPL disseminates news from NIAID through the *NIH Public Bulletin*.

OCPL recently has become involved in outreach activities related to the construction of several NIAID-funded biosafety laboratories. Most prominent among these activities is the neighbor outreach program in Hamilton, Montana, where a new Integrated Research Facility is planned for construction at NIAID's Rocky Mountain Laboratories (RML). A database of RML neighbors has been established so RML can communicate with them rapidly regarding issues related to ongoing activities and new construction at RML. In addition, RML has established a Community Liaison Group that meets regularly and receives updates about plans for development on the RML campus.

In addition, RML recently sponsored two informational symposiums for the community. The symposia combined the talents of local health experts and research scientists from NIAID in Bethesda, who shared the stage in presenting information to the community and answering their questions. The symposium on West Nile virus infection drew approximately 200 community members, including the governor of Montana.

The second symposium on pandemic influenza was attended by approximately 100 community members. RML also collaborated with the State public health agency to share a video of the symposium with more than 50 county and tribal health offices. A DVD of the influenza symposium was sent to the Montana Department of Public Health and Human Services to circulate to about 50 of their health jurisdictions.

RML also presents educational programs for children in three of the local middle schools in the area. The program is called the “Biomedical Research After School Scholars,” or BRASS, program. Most recently, five different classes were given on different topics in biomedical research, such as cell biology and immunology, to seventh and eighth graders.

OCPL has been involved in the outreach efforts of NIAID’s Dale and Betty Bumpers Vaccine Research Center (VRC) as well. The VRC is the first facility at NIH dedicated solely to vaccine research and production. To help the Center with its recruiting efforts for HIV vaccine trials, including the recruitment of underrepresented groups of volunteers, OCPL is proposing volunteer stories to local news media, helping to develop recruitment ads, and coordinating the development of informational materials that can be used by both the VRC and the NIAID-supported extramural HIV Vaccine Trials Network.

NIAID’s Division of AIDS is conducting a national HIV Vaccine Communications Campaign (HVCC) to create a supportive environment for HIV vaccine research. The campaign is designed to create a dialogue to help the public better understand the research, support it, and support those who volunteer for clinical trials. The Institute implemented a qualitative comprehensive research effort, including both primary research (for example, 28 focus groups representing communities most affected by HIV/AIDS) and secondary, or existing, research.

A national survey was conducted in which the attitudes and knowledge about HIV vaccine research were evaluated in the general population as well as in segmented groups of African-Americans, Hispanics/Latinos, and men who have sex with men (MSM). Results of the survey show that misinformation and distrust continue to present formidable barriers to support for HIV vaccine research and that low public awareness and knowledge of HIV vaccine research must be addressed to develop and sustain HIV vaccine clinical research efforts. NIAID staff used the research findings to identify key messages and formulate a campaign strategy that would be both effective and powerful. The HVCC key messages include 1) currently there is no HIV preventive vaccine; 2) only HIV-negative individuals may participate in HIV preventive vaccine trials; 3) a person cannot get HIV from the vaccines being tested; 4) in order for us to develop an HIV vaccine that works for all populations, all populations must participate in clinical trials; and 5) HIV vaccines are our best hope to end the HIV pandemic.

Another major activity of the HVCC is to coordinate activities for the annual HIV Vaccine Awareness Day (HVAD) on May 18th. HVAD was established as a day to acknowledge and thank all the volunteers and researchers involved in HIV vaccine research. Community activities and media events around the country highlight research advances, address challenges associated

with HIV/AIDS, and recognize volunteers who have participated in HIV vaccine clinical trials.

The HVCC also sponsors the Community Education and Outreach Partnership Program (CEOPP). This program was designed to create local and national partnerships aimed at increasing the campaign's ability to provide messages to high-risk populations, specifically African Americans, Hispanics/Latinos, and

MSM; ensure the inclusion of HIV vaccine research information in prevention, care, and treatment programs/curricula/literature; eliminate myths, misconceptions, misperceptions, and misinformation relating to HIV prevention vaccine research; and measure the effectiveness of campaign messages. In 2004, 8 national and 20 community organizations were awarded CEOPP subcontracts.

RESEARCH PLANNING

NIAID has a long-standing tradition of rigorous and prospective research planning, involving the development and prioritization of specific research initiatives on an annual basis and long-range strategic planning. NIAID's planning process was cited as a model by the Institute of Medicine in its 1998 report, *Scientific Opportunities and Public Health Needs: Improving Priority Setting at the National Institutes of Health*. The two pillars of this research planning process are the annual Winter Program Review (WPR) and the Summer Policy Retreat (SPR).

Program Reviews

NIAID's annual program reviews provide an opportunity to focus on future research opportunities and to review proposed research initiatives for new and ongoing research programs.

The specific objectives of the annual program reviews are to:

- Identify major public health, scientific, legislative, and budget directions that will influence NIAID programs;
- Discuss the scientific framework for and priority of new and ongoing research programs in the context of the above factors; and
- Use this information to make decisions about research activities and initiatives to be implemented in the future budget year.

Policy Retreats

The planning process is further enriched through annual policy retreats that provide opportunities to:

- Focus on broad scientific issues, opportunities, gaps, and directions;

- Identify the basis for scientific opportunities and gaps;
- Ensure that scientific planning addresses the interests and priorities of the Congress, the Administration, the Department of Health and Human Services (DHHS), and the NIH Director;
- Propose approaches for responding to newly identified opportunities and needs;
- Identify the implications of changes in scientific or programmatic direction; and
- Prioritize newly identified opportunities and needs within the future budget year.

Throughout the year, NIAID convenes scientific workshops, blue ribbon panels, and program reviews to evaluate progress and to determine future needs and opportunities for the many diseases and areas of research within the Institute's purview. The NIAID Director and each research division consult extensively with NIAID stakeholders, including scientific experts, professional societies, and patient advocacy groups, to develop long-range strategic plans as well as specific research initiatives. Areas of emphasis articulated in strategic plans, as well as those identified by DHHS, the NIH, Congress, the White House, and others, also help shape the Institute's decision-making and priority-setting process for new and continuing research programs.

Planning for future research initiatives is a multistep process that begins 2 years in advance of the projected implementation date. At each step in the process, the concepts for research initiatives are reviewed and refined. Concepts are first subjected to internal discussion during the annual program review, followed by a second level of review and clearance by the National Advisory Allergy and Infectious Diseases Council. Approved concepts are then developed by NIAID staff into various forms of grant and

contract solicitations and announced to the scientific community. Proposed research projects are then peer-reviewed and awarded on the basis of scientific merit, program relevance, and need.

Strategic Planning

NIAID's comprehensive strategic plan, *NIAID: Planning for the 21st Century*, is the product of an intensive effort that included a task force of national experts. The plan describes broad-based priorities to guide NIAID programs, policies, and initiatives through the next 3 to 5 years. The cornerstones of the plan are (1) immune-mediated diseases, (2) human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), (3) emerging infectious diseases and global health, and (4) vaccines. The full text of the plan can be accessed at www.niaid.nih.gov/strategicplan.

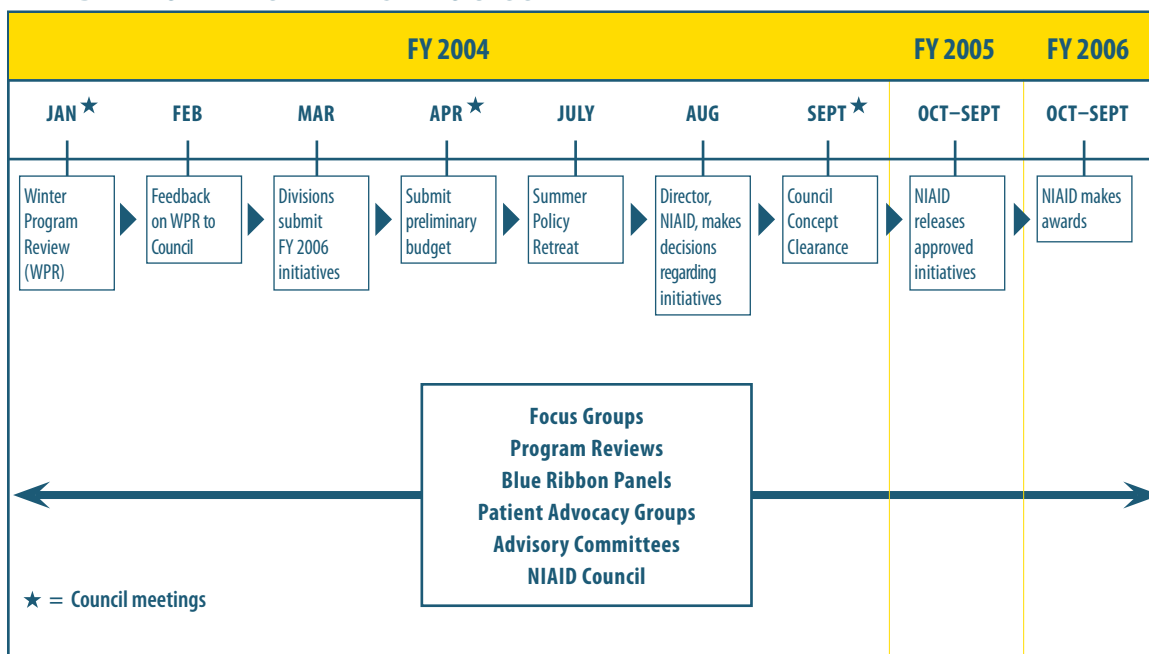
The Institute's guiding principles for global health research are articulated in the *NIAID Global Health Research Plan for HIV/AIDS, Malaria, and Tuberculosis*. This plan identifies short-term, intermediate, and long-term research goals to address these devastating international killers. The plan can be accessed at www.niaid.nih.gov/publications/globalplan.htm.

Since the anthrax mail attacks of 2001, biodefense research has become a major component of NIAID's mission. The vigorous growth of the NIAID biodefense program is guided by expert recommendations and an intricate strategic planning process. In 2002, NIAID convened the first Blue Ribbon Panel on Bioterrorism and Its Implications for Biomedical Research to assist in developing the *NIAID Strategic Plan for Biodefense Research*, the *NIAID Biodefense Research Agenda for CDC Category A Agents*, and the *NIAID Biodefense Research Agenda for Category B and C Priority Pathogens*. The strategic plan

emphasizes basic research on microbes; host defense mechanisms; and the development of drugs, vaccines, and diagnostics. The biodefense research agendas articulate immediate and longer term goals for research on Category A pathogens, which include smallpox, anthrax, Ebola virus, plague, botulinum toxin, tularemia, Marburg virus, Rift Valley fever, and Lassa virus; and goals for research on Category B and C priority pathogens. The agendas also address the research resources, facilities, and scientific manpower needed to conduct basic and applied research on these potential agents of bioterrorism. Both the strategic plan and the research agendas can be accessed at www.niaid.nih.gov/publications/bioterrorism.htm. Tremendous progress has been made since these reports were first released. NIAID has increased the breadth and depth of biodefense research and has made progress in meeting the specific goals of the Blue Ribbon Panel. The *NIAID Biodefense Research Agenda for CDC Category A Agents Progress Report* describes the progress made toward addressing the immediate goals outlined in the research agenda and can be accessed at www2.niaid.nih.gov/biodefense/research/category_a_Progress_Report.pdf.

Another important strategic planning effort focuses on how to further stimulate research activities to address health disparities. The *NIAID Strategic Plan for Addressing Health Disparities* articulates specific action plans for reducing disparities through (1) research on HIV/AIDS, transplantation, autoimmune diseases, tuberculosis, hepatitis C virus, and sexually transmitted diseases; (2) support for research infrastructure and research training; and (3) support for community outreach projects. The full text of the health disparities strategic plan can be accessed at www.niaid.nih.gov/healthdisparities/niaid_hd_plan_final.pdf.

NIAID PRIORITY-SETTING PROCESS



DIVISION OF ACQUIRED IMMUNODEFICIENCY SYNDROME

Mission

The Division of Acquired Immunodeficiency Syndrome (DAIDS) was established in 1986 to help end the HIV/AIDS epidemic by increasing basic knowledge of the pathogenesis and transmission of the human immunodeficiency virus (HIV), supporting the development of therapies for HIV infection and its complications and co-infections, and supporting the development of vaccines and other prevention strategies. To accomplish this, DAIDS plans, implements, manages, and evaluates programs in fundamental basic research; discovery and development of therapies and treatment strategies for HIV infection; its complications and co-infections; and discovery and development of vaccines, topical microbicides, and other prevention strategies. Staffed by over 120 employees, DAIDS is comprised of three main scientific programs—the Basic Sciences Program, the Vaccine and Prevention Research Program, and the Therapeutics Research Program.

Scientific Areas of Focus

Basic Research

HIV pathogenesis research increases our understanding of the biology of HIV by studying the virus' life cycle, virus-host interactions, and mechanisms of disease progression and transmission. HIV pathogenesis research also supports studies of how the immune system responds to the virus. Epidemiologic and natural history research provide information about HIV biology and clinical course of HIV in human populations, which enhances understandings of risk factors for HIV transmission and development and progression of HIV disease. Knowledge gained from these studies enhances researchers' abilities to create new agents and vaccines to combat HIV infection.

DAIDS is studying the natural history of HIV progression in men and women through its cohort studies. The Women's Interagency HIV Study (WIHS) is a collaborative, multisite longitudinal study designed to investigate the impact of HIV infection on women in the United States (<http://statepiaps.jhsph.edu/wihs>). The Multicenter AIDS Cohort Study (MACS) is an ongoing study of the natural history of HIV infection in homosexual men (<http://statepi.jhsph.edu/mac/mac.html>). MACS began in 1983 and was able to capture information about a large number of men who seroconverted while enrolled in the study. The Women and Infants Transmission Study (WITS) examines the natural history of HIV disease in the context of pregnancy, focusing on clinical, laboratory, and psychosocial aspects of maternal/infant transmission. WITS currently is investigating the long-term consequences of exposure to HIV and antiretrovirals in the children born during the study. Programs that study men and women separately give researchers the ability to make gender-based comparisons, thereby adding value to the analyses.

DAIDS also supports a large portfolio of investigator-initiated grants in HIV pathogenesis in a variety of areas, including mechanisms of viral entry and infection; structure, function, and mechanism of action of viral genes and proteins; roles of cellular accessory molecules in replication; immunologic and virologic events controlling primary infection and formation of latent reservoirs; development of *in vitro* and *ex vivo* assays to monitor virus growth, immune responses, and reservoir status during HIV disease; animal models; and genetic analysis of host factors that modulate viral infection or disease progression. These grants serve as a source of new knowledge that fuels the discovery of new drugs and vaccine concepts.

To further stimulate the pursuit of new ideas, DAIDS funds a number of targeted programs, such as the Innovation Grants for AIDS

Research Program, which provides limited funds for 2 years to help advance novel ideas that lack extensive preliminary data. The Novel HIV Therapies: Integrated Preclinical/Clinical Program is another example of how DAIDS supports the discovery, development, and evaluation of innovative HIV treatment concepts through multidisciplinary research and formal corporate partnering. The Centers for AIDS Research program, also supported by DAIDS, provides administrative and resource support and emphasizes the importance of translational research and collaborations between basic and clinical investigators.

To assist the research community, NIAID supports the NIH AIDS Research and Reference Reagent Program, which is now in its 16th year of operation. The Reagent Program continues to provide the scientific community worldwide with a critical and unique resource for biologics and chemicals.

The Division's basic research efforts have yielded significant scientific information about the basic biology of HIV and the immune response to HIV infection. For example, DAIDS-funded investigators have identified the critical steps of how HIV uses the host machinery to enter and exit the cell, as well as the existence of multiple, persistent HIV reservoirs even with the use of highly active antiretroviral therapy (HAART). Although much has been learned in recent years, questions remain about the molecular interactions involved in the regulation of HIV expression and replication and about why the host immune response is not fully effective in controlling the infection. Information about how the virus attacks the body and how the body defends itself is critical to providing additional targets against which therapeutic interventions and vaccines can be directed.

Therapeutics

In order to foster development of new HIV therapies, DAIDS supports research on potential

new cellular and viral therapeutic targets, as well as new approaches to validate targets. The areas of research include identifying molecules that could effectively block HIV replication, improved formulations of existing agents, approaches to restore the immune system of HIV-infected individuals, molecular and genetic approaches to protect susceptible uninfected cells, combination regimens that impede the emergence of viral resistance, and assays to measure restored immunity of HIV-infected individuals. Clinical studies help determine which new agents are effective against HIV and its associated complications and co-infections, and also clarify how best to use these drugs. Investigations include basic research and drug discovery, preclinical development of candidate therapeutics, and advanced clinical testing in humans.

The evaluation of new drugs and therapeutic agents in people is a critical aspect of therapeutic research. Clinical studies define new agents that are effective against HIV and its associated opportunistic infections and co-infections and clarify how best to use these drugs. DAIDS supports clinical therapeutic research in adults and children through several large clinical trials networks, including the Adult AIDS Clinical Trials Group (<http://aactg.s-3.com>), the Pediatric AIDS Clinical Trials Group (<http://pactg.s-3.com>), the Terry Bein Community Programs for Clinical Research on AIDS (www.cpcra.org), and the Acute Infection and Early Disease Research Program (<http://www.aiedrp.org>).

DAIDS-sponsored therapeutics research already has had a dramatic impact on our understanding of the pathogenesis and clinical management of HIV infection over the past decade. Studies conducted by DAIDS-funded clinical trials research networks have (1) helped to define national and international guidelines for the treatment of primary HIV infection and associated opportunistic infections and co-infections, as well as prophylactic regimens for these secondary infections; (2) identified

biological markers such as CD4+ counts and viral load for predicting a drug's effectiveness and disease progression; and (3) demonstrated the use of antiretroviral drugs for preventing mother-to-child transmission (MTCT) of HIV.

More recent studies have shown that HAART regimens, including reverse transcriptase and potent protease inhibitors, are capable of suppressing HIV viral load to undetectable levels in many infected individuals and partially restoring immune function. Such regimens have had a dramatic impact on HIV mortality in this country. Nonetheless, treatment failures occur as a result of the development of resistance or noncompliance with complicated and often toxic regimens. Moreover, damage to the immune system is incompletely reversed. Thus, there is an ongoing, urgent need for new therapeutic agents and regimens, new ways to boost immunity, and ways to rebuild and replace immunity lost to HIV infection. In addition, DAIDS is developing strategies to address critical questions regarding the long-term effects of antiretroviral therapy and the most optimal approaches to medical management, especially to prevent MTCT.

Vaccine and Prevention Research

The discovery and development of an HIV/AIDS vaccine for the prevention of HIV infection and AIDS is a high priority of the NIAID. Through a balanced HIV program that integrates both basic research and empiric testing of candidate vaccines, NIAID supports a broad spectrum of research and development on HIV/AIDS vaccines. Preclinical vaccine research and development examines new vaccine concepts or approaches and new ways to deliver HIV antigens to people and to safely induce a potent anti-HIV immune response. Studies in animal models are aimed at defining how a vaccine could protect the host.

Clinical evaluations in humans provide the only way of determining whether a vaccine candidate could trigger a safe and effective anti-

HIV response in people. NIAID-supported clinical trials of preventive HIV vaccines are carried out in the HIV Vaccine Trials Network (HVTN) (www.hvtn.org). HVTN conducts all phases of clinical trials to determine the safety, immunogenicity, and efficacy of candidate preventive HIV vaccines. Started in 2000, it has made progress towards its goal of developing and conducting a comprehensive HIV vaccine clinical research agenda that addresses scientific and public health needs and builds on scientific opportunities in the field of HIV vaccine research. HVTN has undergone significant expansion to support international trials, instituted highly functioning protocol development teams, developed new vaccine concepts and advanced new protocols, reorganized laboratory programs, and developed an extensive training program. (Additional HVTN information is located in the Vaccine Research and Development section of Selected Scientific Areas of Research on page 127.)

Vaccine research and development are supported through an extensive portfolio of investigator-initiated research in basic virology, immunology, and microbiology. Several DAIDS programs support the interface of preclinical and clinical research. These resources stimulate the development of new vaccine concepts and ensure a rational, deliberate process for moving concepts through to clinical trials. Among the vaccine research programs supported by DAIDS that encourage development along various stages of the vaccine pipeline are the Innovation Grants for Approaches in HIV Vaccine Research Program, which encourages novel and innovative concepts in vaccine discovery and development; the HIV Vaccine Research and Design Program, which supports concepts that have evolved beyond early testing and "matured" innovation grants; and the Integrated Preclinical/Clinical AIDS Vaccine Development Program, which supports the iterative processes of vaccine concept refinement and testing. Through this program, research groups investigate promising vaccine concepts

that are amenable to product development and are likely to lead to preliminary studies in humans. In addition, HIV Vaccine Design and Development Teams, consisting of consortia of scientists from industry and/or academia, identify specific promising vaccine concepts amenable to targeted development.

NIAID also supports comprehensive research on other biomedical/behavioral prevention approaches, including the prevention of MTCT of HIV, topical microbicides, interventions that reduce behaviors that expose people to HIV, programs to reduce intravenous drug abuse, measures to control other sexually transmitted diseases (STDs), and antiretroviral therapies that may reduce the spread of HIV from infected people to their partners.

Non-vaccine HIV prevention research is conducted primarily through the HIV Prevention Trials Network (HPTN) (www.scharp.org/hptn). The HPTN, formed in 2000 with additional support from the National Institute of Child Health and Human Development, the National Institute of Mental Health, and the National Institute on Drug Abuse, is a global, multicenter network dedicated to nonvaccine prevention research. Additional HPTN information is located in the AIDS section on page 41.

The Division's comprehensive vaccine and prevention program has led to a number of significant scientific advances in vaccine and prevention research. In the past, NIAID-supported researchers have improved the ability of vaccines to induce an antibody response by modifying the envelope protein, further explained the envelope structure of HIV, advanced understandings of the role of cellular responses in controlling HIV, developed improved assays for measuring cytotoxic T lymphocytes, developed new and better animal models for testing candidate vaccines, and evaluated promising candidates in animal and clinical studies.

To accelerate identification of effective vaccine candidates, future studies will address the significance of latently infected resting T cells, study immune responses induced by current vaccine candidates, and assess the impact of HIV and human leukocyte antigen diversity. In other prevention research, new microbicides will be evaluated for their safety, acceptability, and ability to prevent the sexual transmission of HIV. Moreover, building on past research that identified an inexpensive regimen to reduce HIV transmission at birth, NIAID will continue to evaluate other practical regimens for preventing MTCT of HIV, especially during breastfeeding.

Lastly, because the majority of new infections are occurring in the developing world, NIAID's prevention and treatment research activities are conducted on a global scale. In fiscal year 2001, NIAID launched the Comprehensive International Program of Research on AIDS (CIPRA). CIPRA provides long-term support directly to developing countries to plan and implement a comprehensive HIV/AIDS prevention and research agenda relevant to their populations and to strengthen the infrastructure required to carry out this research. As their national research capacity grows, countries can seek renewable CIPRA funding for multidisciplinary research projects and/or clinical trials for HIV prevention and/or treatment. For more information, visit the Web site at www.niaid.nih.gov/daids/cipra.

Advisory Groups

DAIDS assesses ongoing needs in biomedical research as well as requirements for outreach activities and training scientific investigators. As part of this process, DAIDS works with a number of advisory groups and community and health professional organizations to help evaluate and redirect the Division's global research programs by identifying research needs, setting priorities, and planning future programs. These advisory bodies include the AIDS Research Advisory Committee (ARAC) and the AIDS Vaccine

Research Working Group (AVRWG). The ARAC advises the Directors of DAIDS and NIAID on all aspects of the research portfolio, reviews progress and productivity of ongoing efforts, provides assistance in identifying critical gaps/obstacles to progress, and approves of concepts for new initiatives. The AVRWG assists in developing a comprehensive research program for expediting the discovery and development of an HIV vaccine.

Collaborations

DAIDS actively supports and promotes public and private-sector alliances to maximize available research opportunities and resources. Our commitment to identify effective prevention strategies and treatments has led to a steady increase in international activities, particularly in the developing world, where there is critical need for cost-effective prevention, treatment, and care. These efforts, in particular, necessitate collaboration with other Federal and non-Federal agencies, given the complexity of global research efforts. As a result, NIAID has forged collaborations with the Centers for Disease Control and Prevention (CDC) and Department of Defense (DoD) in order to bring together the vast expertise, experience, and resources of each organization and help foster coordination and efficiency. The Partnership for AIDS Vaccine Evaluation (PAVE) is one example of collaboration between NIAID, CDC, and DoD that was established as a way to accelerate global HIV vaccine research efforts and increase efficiency and cost effectiveness through shared laboratory capabilities, clinical trial sites, and compatibility of protocols and data.

Domestic and International Activities

With the growing global impact of HIV/AIDS, there is a critical need for cost-effective prevention and treatment strategies in limited-resource regions of the world where more than 95 percent of HIV infections occur. With the explosive growth of new infections

in the developing world, most of DAIDS-funded clinical research programs now have an international component. DAIDS supports research at academic and medical research centers, and collaborates with research and development companies worldwide. Many of DAIDS' activities support countries listed in the President's Emergency Plan for HIV/AIDS Relief (PEPFAR), which include Cote d'Ivoire, Botswana, Ethiopia, Guyana, Haiti, Kenya, Mozambique, Namibia, Nigeria, Rwanda, South Africa, Tanzania, Uganda, Vietnam, and Zambia. While domestic research continues to focus on identifying the most effective treatment and prevention options for adults, adolescents, and children, internationally-focused activities are designed to define global research priorities, ensure the clinical relevance of future vaccine and prevention strategies to human populations most in need, strengthen collaborations with local investigators worldwide, and support training and infrastructure development in developing countries.

Role of Community

DAIDS has long recognized the importance of sustained relationships with the community, which are necessary to help foster and maintain trust and ensure that the research is designed to meet community needs. Each of the clinical research networks supported by DAIDS has a Community Advisory Board (CAB) that works with the leadership of the network on all aspects of the research process, and other CABs that work with each individual research site. The CABs help ensure that the researchers are working in partnership with the community and help to improve communications to the community and from the community to researchers. Community outreach and education are also integral components of the Division's activities.

Major programs supported by DAIDS

- Acute Infection and Early Disease Research Program
- Adult AIDS Clinical Trials Group
- AIDS Research and Reference Reagent Program
- Centers for AIDS Research
- HIV Prevention Trials Network
- HIV Vaccine Design and Development Teams
- HIV Vaccine Research and Design Program
- HIV Vaccine Developmental Resources Contracts
- HIV Vaccine Trials Network
- Innovation Grant Program
- HIV Vaccine Communications Campaign
- Novel HIV Therapies: Integrated Preclinical/Clinical Program
- Integrated Preclinical/Clinical AIDS Vaccine Development Program
- Multicenter AIDS Cohort Study
- Pediatric AIDS Clinical Trials Group
- Simian Vaccine Evaluation Units
- Terry Bein Community Programs for Clinical Research on AIDS
- Women and Infants Transmission Study
- Women's Interagency HIV Study

DIVISION OF ALLERGY, IMMUNOLOGY, AND TRANSPLANTATION

Mission

The human immune system is composed of intricate networks of specialized cells, molecules, and organs that act together to defend the body against foreign invaders such as viruses, bacteria, and fungi that may cause disease. However, aberrant immune responses play a critical role in the development of immune-mediated diseases, which include asthma and allergic diseases; autoimmune disorders; primary immunodeficiencies; and rejection of transplanted solid organs, tissues, and cells. Collectively, these chronic diseases affect tens of millions of Americans, resulting in considerable morbidity, mortality, pain and suffering, and high medical costs. Immune-mediated diseases cross many clinical specialties, and knowledge of the immune system and its role in disease is increasingly important in the clinical management of patients with these disorders.

The past two decades of focused research on the immune system have resulted in major advances in understanding the mechanisms that underlie a range of immune-mediated diseases. These advances in conceptual understanding now provide realistic opportunities for improvement in the diagnosis, treatment, and prevention of many of these diseases. The Division of Allergy, Immunology, and Transplantation (DAIT) (www.niaid.nih.gov/research/dait.htm) promotes and supports a broad range of research that seeks to further our understanding of the immune mechanisms underlying immune-mediated diseases and to translate this basic knowledge to clinical applications that will benefit individuals affected by these diseases. The ultimate goal of DAIT's research program is the development of effective approaches for the treatment and prevention of immune-mediated diseases.

The Division supports research initiated by individual investigators; multidisciplinary program projects that explore the mechanisms of immune-mediated diseases, transplantation immunology, and the basic biology of the immune system; clinical research programs to assess the safety and efficacy of new therapeutic approaches; and interdisciplinary cooperative research centers.

DAIT supports basic, preclinical, and clinical research to enhance our understanding of the causes of immune-mediated diseases and to apply this knowledge to the development of improved approaches to disease diagnosis, treatment, and prevention through demonstration and education research projects. DAIT also supports research that evaluates the effectiveness of behavioral and educational interventions to promote health and prevent disease in defined populations.

DAIT's research programs are placing increasing emphasis on the preclinical and clinical development of new tolerogenic and immunomodulatory approaches for the treatment and prevention of transplant rejection, asthma and allergic diseases, and autoimmune diseases. Another area of program growth involves the application of emerging technologies to further our understanding of immunologic principles and to develop diagnostic and prognostic tools and biomarkers of disease activity and therapeutic effect.

Scientific Areas of Focus

Asthma and Allergic Diseases

Asthma and allergic diseases are among the major causes of illness and disability in the United States. Studies to examine the causes, pathogenesis, diagnosis, treatment, and prevention of asthma and allergic diseases represent a major focus of DAIT's basic and clinical research portfolio. DAIT's national network of Asthma and Allergic Diseases Research Centers focuses on the underlying immune mechanisms involved

in these disorders and on approaches to improve diagnosis and treatment by fostering investigator-initiated projects and supporting cooperative clinical studies. The Inner-City Asthma Consortium (ICAC): Immunologic Approaches to Reduce Asthma Severity, a network of basic scientists and clinical investigators, was established by DAIT in fiscal year (FY) 2002 to evaluate the efficacy of promising immune-based therapies to reduce asthma severity and prevent disease onset in inner-city children. In FY 2004, the ICAC launched a cockroach allergen standardization protocol; a study to evaluate the usefulness of measurements of exhaled nitric oxide in the clinical management of asthma in children; and a birth cohort to investigate the allergic and environmental factors that contribute to the development of asthma in inner-city children.

Autoimmune Diseases

Autoimmune diseases, which result from a disordered attack of the immune system on the body's own tissues, affect an estimated 5 to 8 percent of the United States population and disproportionately afflict women. DAIT supports a broad range of basic and clinical research programs in autoimmunity. Basic research focuses on understanding the genetics of autoimmunity, elucidating the mechanisms of self-tolerance, developing approaches to induce self-tolerance, and characterizing pathways of immune-mediated tissue destruction. Knowledge gained from basic studies provides the rationale for developing clinical tests to diagnose autoimmune diseases and novel treatments for ongoing disease. DAIT supports the Autoimmunity Centers of Excellence, which conduct collaborative basic and clinical research on autoimmune diseases, including single-site and multisite pilot clinical trials of immunomodulatory therapies and mechanism-of-action studies. DAIT also supports the Centers for Autoimmune Disease Prevention, which focuses on advancing knowledge for the prevention of rheumatoid

arthritis and other autoimmune diseases. The goal of the Autoimmunity Prevention Centers is to develop the knowledge base necessary to design preventive interventions that could be administered efficiently and safely. In FY 2004, the Prevention Centers supported 16 pilot projects to test innovative approaches that might lead to the development of novel targets for disease prevention or assays for biomarkers of disease progression.

Basic and Clinical Immunology

The Division's basic immunology investigations focus on the properties, interactions, and functions of immune system cells and the substances produced by those cells. Information generated through this research provides the knowledge base necessary to develop treatment and prevention strategies. To promote research on these fundamental aspects of immune system functioning, DAIT supports multidisciplinary program projects on the biology of the immune system, including the basic biology of immune responses for vaccine research, transplantation immunology and chronic rejection, and autoimmunity. Clinical immunology studies focus on immune-mediated diseases, including autoimmune diseases, asthma and allergic diseases, acute and chronic transplant rejection, and immunodeficiencies. Research in these clinical areas is supported by program projects on mucosal immunity, autoimmune diseases, and methods of immune intervention.

Immune Tolerance

Immune tolerance is a high priority for NIAID, and, as part of a broad-based, long-range plan to accelerate research in this important area, DAIT established the Immune Tolerance Network (ITN). The ITN is an international consortium of more than 80 investigators in the United States, Canada, Europe, and Australia dedicated to the clinical evaluation of novel, tolerance-inducing therapies in autoimmune diseases, asthma and allergic diseases, and rejection of

transplanted organs, tissues, and cells. The goal of these therapies is to “re-educate” the immune system to eliminate injurious immune responses and graft rejection while preserving protective immunity against infectious agents. The ITN also conducts integrated studies on the underlying mechanisms of these approaches and develops and evaluates markers and assays to measure the induction, maintenance, and loss of tolerance in humans. The ITN has established a variety of state-of-the-art core facilities and has supported 18 approved clinical protocols and several additional studies of the immune mechanisms that lead to development, maintenance, or loss of clinical tolerance. Currently, the ITN supports seven clinical trials in solid organ and islet transplantation and two cohort studies to better understand the immune mechanisms involved in the acquisition of spontaneous tolerance to organ grafts. More information about the ITN is available on its Web site at www.immunetolerance.org.

Primary Immunodeficiency Diseases

Primary immunodeficiency diseases (PIDs) are caused by intrinsic defects in the cells of the immune system and are often due to inherited genetic defects. NIAID-supported research in these diseases focuses on understanding the causes and immune mechanisms leading to the development of primary immunodeficiency diseases. This includes identifying pathogenic gene mutations and other contributing etiologies and expanding the genetics knowledge base to improve diagnosis, facilitate genetic counseling and decisionmaking for affected individuals, and provide protective and curative treatments, including gene therapy. In FY 2003, NIAID, with cosponsorship from NICHD, established the Primary Immunodeficiency Diseases Consortium. The Consortium: (1) provides leadership and mentoring; facilitates collaborations; enhances coordination of research efforts; and solicits, reviews, and makes awards for pilot or small research projects; (2)

maintains a primary immunodeficiency diseases registry, which provides data to the research community about the clinical characteristics and prevalence of these diseases; and (3) develops a repository of specimens from subjects with primary immunodeficiency diseases. Additional information on Consortium activities is available on its Web site: www.USIDNet.org. NIAID also supports research in large animal models of primary immunodeficiency diseases, as well as clinical trials to determine the most efficacious bone marrow transplantation regimens in patients with these diseases.

Transplantation

The Division’s research in transplantation immunobiology is focused on understanding the mechanisms whereby the immune system recognizes and either accepts or rejects transplanted organs, tissues, and cells; developing preclinical models to evaluate promising therapies to prevent and treat graft rejection; conducting clinical trials of new therapeutic agents and approaches to improve graft survival and function; and understanding the pathogenesis of chronic graft failure and developing new treatments and preventive strategies. Clinical research to evaluate new therapeutic approaches to improve kidney engraftment and survival is carried out through the Cooperative Clinical Trial in Pediatric Kidney Transplantation. In FY 2004, NIAID, in collaboration with other NIH Institutes, established the Clinical Trials in Organ Transplantation Consortium to improve the success of organ transplants for end-stage organ disease. The goals of the consortium are to identify genetic factors in patients that could help doctors predict transplant outcomes and responses to post-transplant therapy; develop diagnostic tests that enable early detection and ongoing monitoring of immune-related processes; and test the safety and effectiveness of new, less toxic immunosuppressive drugs.

Primary Research Areas

Asthma and Allergic Diseases

- Asthma and Allergic Diseases Research Centers
- Inner-City Asthma Consortium
- Immune System Development and the Genesis of Asthma

Autoimmune Diseases

- Autoimmune Diseases Prevention Centers
- Autoimmunity Centers of Excellence
- Stem Cell Transplantation for Autoimmune Diseases Consortium

Basic and Clinical Immunology

- Cooperative Centers for Translational Research on Human Immunology and Biodefense
- Hyperaccelerated Award/Mechanisms in Immunomodulation Trials
- Vaccine Immunology Basic Research Centers

Immune Tolerance

- Immune Tolerance Network
- Innovative Grants on Immune Tolerance
- Nonhuman Primate Immune Tolerance Cooperative Study Group

Primary Immunodeficiency Diseases

- Primary Immunodeficiency Diseases Consortium
- PID Registry—USIDNET

Transplantation

- Cooperative Clinical Trial in Pediatric Kidney Transplantation
- Clinical Trials in Organ Transplantation
- Genomics of Transplantation Cooperative Research Program

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES

Mission

The Division of Microbiology and Infectious Diseases (DMID) supports extramural research to control and prevent diseases caused by virtually all human infectious agents except HIV. DMID supports a wide variety of projects spanning the spectrum from basic research through applied research, along with the development and clinical evaluation of new drugs, vaccines, and diagnostics. NIAID also funds projects to sequence the full genomes of a number of medically important microbes, which can be exploited in many ways—for example, to trace microbial evolution, to locate targets for vaccine and drug development, and to identify mutations that contribute to drug resistance.

Research areas in basic bacteriology and mycology include molecular structure and function, genetics, biochemical composition, and physiologic and biochemical processes. Studies on these pathogens extend basic insights to identify vaccine candidate antigens and drug targets and to examine mechanisms of infection, pathogenicity, and virulence. Areas of particular interest include streptococci, pneumonia, nosocomial (hospital-acquired) infections, fungal infections, antibiotic resistance, bacterial sexually transmitted infections, and bacterial diarrheas.

Research areas in virology include molecular structure and function, genetics, synthesis, and reproduction of viruses; characterization of viral proteins and nucleic acids; mechanisms of pathogenicity, latency, persistence, and reactivation; interactions with immune systems; and vaccine development. Basic information is being used to combat important viral diseases such as influenza, herpes, congenital cytomegalovirus infection, hepatitis, and viral diarrheas.

Research on parasites involves the application of biochemical, genetic, and immunologic approaches. Studies of parasites are leading to the identification of protective and diagnostic antigens and to the development of more effective drugs. In addition, studies of arthropod vectors are aimed at controlling the transmission of important pathogens such as the malaria parasite.

One of the primary goals of the Division is to develop new and improved vaccines and strategies for vaccine delivery for the entire spectrum of infectious agents: bacteria, viruses, fungi, and parasites. Since 1981, DMID has supported a program for the accelerated development of new vaccines to direct advances in molecular biology, immunology, genetics, and epidemiology. An integral component of these efforts is vaccine safety, which is evaluated in every vaccine clinical trial sponsored by NIAID.

DMID also supports numerous efforts aimed at developing more effective diagnostic tools for infectious diseases. Examples include diagnostic tests for STIs and Lyme disease and the development of antimicrobial resistance markers.

Finally, DMID maintains a drug development program that supports research at three levels: drug discovery (accomplished by screening and by targeted molecular research), preclinical evaluation (in animal models of human infections), and clinical trials (evaluation of new therapies in humans).

Scientific Areas of Focus

Biodefense

As concern grows about the use of biological agents in acts of terrorism and war, Federal agencies are evaluating and accelerating measures to protect the public from the health consequences of such an attack. Our ability to detect and prevent infections that emerge as a result of bioterrorist incidents depends to a large degree on the state of biomedical science. Basic

and applied research supported by the NIH complements the efforts of other Federal agencies by developing the essential tools—diagnostics, therapeutics, and vaccines—that are needed by physicians, nurses, epidemiologists, and other public health workers to prevent and control outbreaks of disease. NIAID is the primary NIH Institute that supports and conducts research on the diagnosis, prevention, and treatment of infections caused by a wide variety of emerging pathogens, including those that could be intentionally introduced.

In response to the need for rapid development of resources for biodefense, NIAID continues to expand its research related to potential agents of bioterrorism as part of a broad research agenda involving other agencies within the Department of Health and Human Services and the Department of Defense. The components of the NIH's biodefense research program include development of biodefense-relevant diagnostics, therapeutics, and vaccines, as well as genomics, basic research on potential agents of bioterrorism, and infrastructure to support advanced research. Recent NIAID programmatic accomplishments include support for bioinformatics and proteomic resource centers; expansion of the Vaccine and Treatment Evaluation Units to accommodate testing of vaccines such as those for smallpox and anthrax; development of several new animal models for diseases caused by Category A, B, and C agents; support for grants and public-private partnerships for early product development through clinical trials of biodefense vaccines and drugs; a centralized repository to acquire, authenticate, store, and distribute NIAID Category A, B, and C agents to the scientific community for use in research and product development; and the expansion of research capacity through the multimillion dollar Research Centers of Excellence (RCEs) and National and Regional Biocontainment Laboratories (NBLs and RBLs) across the United States, which will provide critical resources for biodefense and emerging infectious disease research.

Emerging and Re-emerging Infectious Diseases

Emerging infectious diseases include outbreaks of previously unknown diseases or known diseases whose incidence in humans has significantly increased in the past two decades. Re-emerging diseases are known diseases that have reappeared after a significant decline in incidence. Recent outbreaks of severe acute respiratory syndrome (SARS) and avian influenza in Asia and monkeypox in the United States are examples of emerging infectious diseases, while tuberculosis and pertussis are examples of diseases that have re-emerged after a period of decline. Factors involved in the emergence and re-emergence of infectious diseases include evolution of microbes; changes in vaccine compliance; overuse of antimicrobials; and changes in the interactions between humans and the environment due to human population growth, density, and contact with animal vectors or animals that may serve as disease reservoirs.

Both emerging and re-emerging diseases have significant implications for domestic and global health. DMID supports a broad spectrum of basic research on infectious diseases, including studies of epidemiology; pathogenesis; transmission and microbiology of emerging infectious diseases; and applied and clinical studies to develop and test vaccines, diagnostics and therapeutics for these diseases. Examples of DMID-supported research on emerging infectious diseases include robust research programs in SARS, West Nile virus, Lyme disease, and influenza. In 2003, DMID also provided funding for multiple RCEs, NBLs and RBLs across the United States, where scientists will be able to safely conduct critical research on emerging infectious diseases and NIAID Category A–C Priority Agents.

Vaccine Research and Development

DMID supports an active program of basic and applied research for the accelerated development of new vaccines, taking advantage of advances

in molecular biology, immunology, genetics, and epidemiology. Research conducted under this program contributes to the development of new vaccines for a wide variety of bacterial, viral, and parasitic diseases, including SARS, malaria, West Nile virus, herpes, and pneumococcal pneumonia. DMID also supports research to develop novel vaccine delivery methods, such as transcutaneous skin patches and nasal vaccines. One example of NIAID's success in developing innovative vaccines is the recent licensure by the Food and Drug Administration of the FluMist intranasal influenza vaccine, for which much of the research and early development was supported by NIAID. DMID also supports a large national and international network for clinical trials of safety and efficacy of vaccines. Recent expansions of the network will allow more trials focused on specific populations and larger clinical trials, including those for biodefense vaccines. DMID's *Jordan Report*, now in its 20th anniversary edition, is a unique resource developed by the Division to inform the public health community and the general public of recent developments and the state of the science in vaccine research. This report can be viewed online at www.niaid.nih.gov/dmid/vaccines/jordan20.

Antimicrobial Drug Resistance

Emergence of drug-resistant infectious agents is becoming an increasingly important public health concern. Rapid evolution of microbes and misuse of antibiotics are major contributors to the rising number of resistant pathogen strains. Tuberculosis (TB), gonorrhea, malaria, and childhood ear infections are just a few of the diseases that have become more difficult to treat because of the emergence of drug-resistant pathogens. Antimicrobial resistance is becoming a factor in virtually all hospital-acquired infections. Also, drug resistance that was almost exclusively hospital- or healthcare-associated is appearing and originating with increasing frequency in the community, such as community acquired methicillin resistant *Staphylococcus aureus*. Many

physicians are concerned that several bacterial infections soon may be untreatable with currently available drugs.

NIAID funds a diverse portfolio of grants and contracts to study antimicrobial resistance in major viral, bacterial, fungal, and parasitic pathogens, including antimicrobial resistance among the major healthcare-associated bacterial pathogens. Specifically, NIAID supports investigator-initiated research on the molecular mechanisms responsible for drug resistance, as well as research to develop and evaluate new or improved therapeutics for disease intervention and prevention. Studies on several key organisms of interest seek to define how bacterial pathogens acquire, maintain, and transfer antibiotic-resistant genes. In August 2004, NIAID held the second Summit on the State of Anti-Infective Development to address the important issue of antimicrobial availability and to help determine the best ways for NIAID to address the key needs. NIAID also continues to participate in an interagency task force for the development of public health strategies for antimicrobial resistance. *The Public Health Action Plan to Combat Antimicrobial Resistance*, developed by the task force, describes issues, goals, and action items in surveillance, prevention and control, research, and product development, as well as a plan for interagency and industry coordination in addressing this critical health issue. The action plan is available online at www.cdc.gov/drugresistance/actionplan/index.htm.

Global Health

NIAID has developed a comprehensive global health research plan to address key issues in international health. Many of these activities focus on vaccine development. Genomics, microbial physiology, epidemiology and natural history, transmission/vector control, and development of improved diagnostics and therapies also are important areas of emphasis. Diseases of international health importance present additional scientific and logistical

challenges, such as access to endemic sites and populations. The Institute supports field-based research through investigator-initiated grants, disease-specific initiatives, and special programs, such as the International Collaborations in Infectious Diseases Research and the Tropical Medicine Research Centers.

DMID supports a broad portfolio of research in both TB and malaria. Areas of emphasis in DMID's TB research include basic biology of the TB pathogen and drug-resistant strains, disease progression, diagnostics, vaccines, therapeutics, epidemiology, and genomics. The NIAID Tuberculosis Research Unit supports an international, multidisciplinary team of collaborators to translate basic research findings into clinical studies. Current research activities sponsored by NIAID for malaria include drug development, pathogenesis research, vaccine development, epidemiology, and vector control. NIAID also supports the International Collaborations in Infectious Diseases Research program and the Tropical Medicine Research Center program to develop and evaluate new diagnostics, prevention, control, and therapeutic methods for tropical infectious diseases. These programs also provide training to international scientists and build capacity for independent research at overseas field sites.

Sexually Transmitted Infections

Sexually Transmitted Infections (STIs) are a critical global health priority for two reasons: their devastating impact on women and infants and their interrelationship with AIDS. Scientists now believe that people who have STIs are at an increased risk of contracting HIV/AIDS. DMID's STI research emphasis is on vaccine development and on clinical, epidemiologic, and behavioral investigations directed toward strategies for primary and secondary prevention of STIs and conditions associated with having STIs, including pelvic inflammatory disease, infertility, ectopic pregnancy, cervical cancer, fetal wastage, prematurity, congenital infection, and

the spread of HIV. A public-private partnership between NIAID and GlaxoSmithKline currently is supporting a phase III clinical trial for a new genital herpes vaccine for women. This has the potential to prevent a disease that is estimated to affect 45 million people in the United States aged 12 years and older and has significant health implications for infants. NIAID also supports a topical microbicide research effort to prevent STIs; this effort encompasses basic product development and clinical research.

Pathogen Genomics

In 1995, the first microbe-sequencing project, *Haemophilus influenzae* (a bacterium causing upper respiratory infection), was completed with a speed that stunned scientists. Encouraged by the success of this initial effort, researchers have continued to sequence an astonishing array of other medically important microbes. NIAID has made a significant investment in large-scale sequencing projects and includes projects to sequence the full genomes of many pathogens, including the bacteria that cause TB, gonorrhea, chlamydia, cholera, agents of bioterrorism, and viruses that cause flu. In addition, NIAID collaborates with other funding agencies to sequence larger genomes of pathogenic fungi, protozoan pathogens such as the organism causing malaria, and invertebrate vectors of infectious diseases.

The availability of microbial and human DNA sequencing in publicly-accessible databases has opened up new opportunities and allows scientists to examine functional analysis of genes and proteins in whole genomes and cells, as well as the host immune response and an individual's genetic susceptibility to pathogens. When scientists identify microbial genes that play a role in disease, drugs can be designed to block the activities controlled by those genes. Because most genes contain the instructions for making proteins, drugs can be designed to inhibit specific proteins or to use those proteins as candidates for vaccines. Comparative genomic analysis of

microbes also can be used to study the spread of a virulent or drug-resistant form of a pathogen.

NIAID is committed to continuing its support to sequence the genomes of microbes as well as increasing its support for functional genomics and proteomics, decoding sequence information, and determining its functional sequence. Moreover, NIAID is committed to facilitating the access and distribution of genomic

resources and technologies to the research community for functional genomic analysis of microbial pathogens, as well as to supporting the development of bioinformatic and computational tools and databases to allow investigators to have easy access to sequence and functional data for analysis. In summary, DMID supports a breadth of research activities on a variety of pathogens of importance in basic microbiology and infectious diseases.

DIVISION OF INTRAMURAL RESEARCH

Mission

Scientists in NIAID's Division of Intramural Research (DIR) (www.niaid.nih.gov/dir) conduct laboratory and clinical research covering a wide range of biomedical disciplines related to infectious diseases, immunology, and allergy. For example, DIR scientists conduct basic laboratory investigations to understand the biology and genetics of the viruses, bacteria, parasites, and fungi that cause infectious diseases. They also study the ticks, mosquitoes, fleas, and flies that transmit diseases such as West Nile fever, plague, and malaria. In addition, DIR has a large program focused on investigations of prion diseases, such as "mad cow" disease and chronic wasting disease of deer and elk, which are caused by a transmissible agent that has little in common with conventional infectious microbes.

Much of the research in DIR involves investigation of the multitude of interacting cells, antibodies, proteins, and chemicals that compose the immune system. A fundamental understanding of this intricate system is key to the development of therapies and vaccines for infectious diseases and critical to deciphering and treating immune system disorders—from mild allergies to life-threatening immunodeficiencies. The ultimate goal of the Division's research is to contribute to the development of new and improved therapies, diagnostics, and vaccines that will improve health, save lives, and enhance the quality of life in the United States and worldwide. This contribution may take the form of delineating a cell signaling pathway, discovering the function of a tick gene, determining the three-dimensional structure of an immune cell receptor, or finding the enzyme malfunction causing a primary immunodeficiency.

Translating laboratory research findings to the clinical arena is accomplished through the

facilities of the Warren Grant Magnuson Clinical Center on the NIH campus. There, physician-scientists treat patients with a variety of diseases, including AIDS, host defense defects, asthma, various parasitic diseases, and disorders of inflammation. NIAID currently has more than 80 active clinical protocols, under which patients participate in studies of new and promising treatments or diagnostic procedures, often derived from ongoing laboratory research efforts.

In addition to conducting innovative scientific studies, DIR researchers devote considerable effort to mentoring young scientists, teaching, and other academic pursuits. Each year, DIR laboratories host hundreds of predoctoral and postdoctoral trainees who are immersed in the superb scientific setting at the NIH while they participate in DIR's basic and clinical research programs.

The Division and its staff of scientists and physicians have received national and international recognition for their outstanding research achievements. Eight members of the current staff have been elected to the National Academy of Sciences, and many staff members have earned prestigious awards for their contributions to science.

Scientific Resources

Each of the 17 DIR laboratories (www.niaid.nih.gov/dir/labs.htm) has project-specific resources that are augmented by the expertise and services provided to all DIR labs by supporting branches. The DIR branches offer access to state-of-the-art technologies for peptide synthesis, protein sequencing, mass spectroscopy analysis of peptides and small molecules, electron microscopy, confocal microscopy, flow cytometry and cell sorting, and DNA microarray. The branches also provide genetically modified (transgenic as well as knockout/knockin) mice, extensive in-house animal breeding and holding facilities (including nonhuman primate), oversight of animal protocols, and support to

scientists conducting animal studies. Animal care facilities, including biosafety level 3 facilities, are maintained in Bethesda, Maryland, and at DIR laboratories in Hamilton, Montana. In addition to the facilities directly managed by NIAID, DIR investigators have access to NIH-wide facilities such as the Mouse Imaging Facility. Investigators wishing to interact directly with other scientists in a very focused setting can do so by joining one of the more than 80 NIH scientific interest groups organized around specialty areas.

Computer linkages for DIR scientists consist of a local area network within NIAID and a wide area network linking DIR scientists to other areas of NIH, such as the computer facilities of the NIH Division of Computer Research and Technology. The computer network also provides quick access to the libraries of the NIH Clinical Center and to the National Library of Medicine and links DIR researchers in the Maryland locations of Bethesda, Rockville, and the Frederick Cancer Research and Development Center and in the Rocky Mountain Laboratories in Hamilton, Montana. Teleconferencing equipment further enhances communications between DIR staff members and their colleagues across the campus and around the world. In addition, DIR investigators communicate with colleagues at the Malaria Research and Training Center in Mali via direct satellite uplinks, which are much faster and more dependable than the local Internet service provider connections.

Scientific Areas of Focus

Immunology Research

Immunology research is inextricably linked to studies of infectious diseases and allergy. In studying immunologic diseases, DIR scientists consider both the normal processes of the immune system and how these processes malfunction in the disease state. Findings from the studies are used in several ways. First, they are used in the development of new or improved vaccines that stimulate the immune system

to recognize and destroy invading organisms. Second, the findings enhance the understanding and development of effective treatments for immunodeficiency diseases in which the immune cells are lacking or performing inadequately. Finally, they can be used in the elucidation and treatment of autoimmune diseases in which the immune cells attack the body's own cells. Current investigations include the following:

- Functional studies of regulatory T cells;
- Innate immune response to pathogenic bacteria;
- Animal models of autoimmune diseases; and
- Novel therapies for primary immunodeficiencies.

Allergy Research

Researchers studying allergic diseases concentrate on asthma; allergic reactions involving the skin, nasal passages, and sinuses; and chronic food allergy. Much of this research focuses on the mast cell, which plays an important role in many allergic disorders and secretes chemicals such as histamine. Histamine is responsible, in part, for triggering the events that cause the visible signs of an allergic reaction, such as hives, difficulty breathing, or a runny nose. Intramural scientists study how mast cells develop, their gene regulation, and their interactions with other cells in the connective tissue. Other projects are concerned with mucous membrane functions in the respiratory tract, both in normal and allergic individuals, and the role of the autonomic nervous system in causing allergic symptoms. Studies include the following:

- Cytokine profiles of allergic diseases;
- Tolerance studies for asthma;
- Development of mast cell lines for use in drug discovery; and
- Pathogenesis of food allergy.

Infectious Disease Research

DIR programs to improve the treatment and control of infectious diseases involve a multidisciplinary approach aimed at increasing our understanding of pathogenic organisms, host response to infection, vector biology, and chemotherapeutics. Studies of the microorganisms—the bacteria, viruses, fungi, and parasites that cause diseases as varied as tuberculosis, AIDS, West Nile fever, and malaria—may reveal opportunities to use drugs to interfere with vital processes within the organism that are necessary for reproduction. Host studies may define the necessary immune response to successfully fight infection and help investigators design effective vaccines, whereas vector studies may reveal new targets for public health interventions. Application of this multidisciplinary approach to investigations of new and re-emerging infectious diseases and biodefense studies is a top DIR priority. DIR scientists are collaborating with colleagues from government, academia, and industry to develop vaccines, diagnostics, and therapeutics for high-priority pathogens and to conduct the basic laboratory research that provides the foundation for product development. In addition, DIR scientists are engaged in collaborative research in a number of developing countries with a high infectious disease burden. Additional information about DIR studies of biodefense research and emerging infectious diseases can be found on pages 54 and 71, respectively. Other ongoing projects in DIR include the following:

- Structured therapy interruption as an AIDS treatment strategy;
- Development of more effective drugs for tuberculosis;

- Pathogenesis and cross-species transmissibility of prion diseases or transmissible spongiform encephalopathies; and
- Genetics of drug resistance, antigenic variation, and disease severity in malaria.

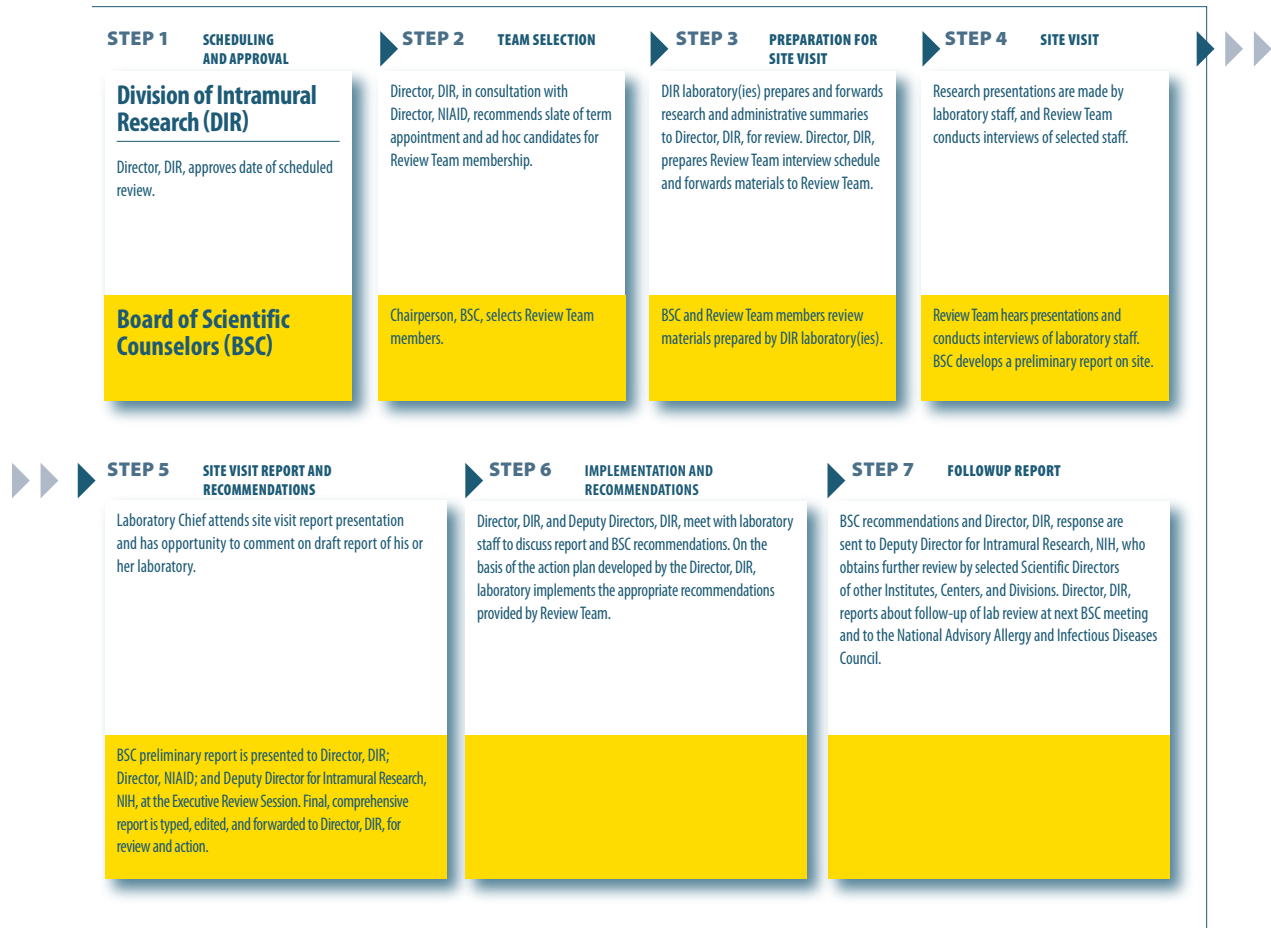
Vaccine Research

Candidate vaccines against many infectious agents of public health importance are undergoing laboratory and clinical testing in DIR. These include vaccines for respiratory and gastrointestinal viruses, hepatitis viruses, and infectious agents that cause common tropical diseases such as malaria and dengue. DIR scientists also are collaborating in the development of vaccines to prevent the natural or deliberate spread of infectious diseases such as smallpox, severe acute respiratory syndrome (SARS), plague, and pandemic influenza. Studies are under way to develop vaccines against pathogenic flaviviruses such as the West Nile virus, St. Louis encephalitis virus, and tick-borne encephalitis virus. Investigations continue toward the development of a vaccine against the respiratory syncytial virus, the principal cause of respiratory disease in infants in the United States and the world. In addition, the parainfluenza viruses, which cause respiratory disease in children and adults, are targets for vaccine development in DIR. For additional DIR information, see page 133.

Laboratory Review Process

The following chart provides information on DIR's laboratory review process:

DIVISION OF INTRAMURAL RESEARCH LABORATORY REVIEW PROCESS



DALE AND BETTY BUMPERS VACCINE RESEARCH CENTER

Mission

The Dale and Betty Bumpers Vaccine Research Center (VRC) (www.vrc.nih.gov) is dedicated to translating the latest knowledge of disease pathogenesis and immunology into new vaccine strategies, thereby providing safe and effective means to prevent and control human diseases. The primary focus of VRC is to conduct research to develop an effective AIDS vaccine. The global epidemic of HIV infection is one of the most significant infectious disease threats to human health. Although new AIDS diagnoses and deaths have fallen significantly in many developed countries, the HIV/AIDS epidemic continues to accelerate in the developing world. There are an estimated 5 million new HIV infections each year, and in 2004 the disease resulted in an estimated 3 million deaths.¹ Beyond the human tragedy of HIV/AIDS, the epidemic poses a significant impediment to the economic growth and political stability of many countries. In developing countries and in segments of the U.S. population, anti-HIV therapies are frequently beyond patients' financial reach. Therefore, effective, low-cost tools for HIV prevention are urgently needed to bring the HIV epidemic under control. A globally effective, accessible vaccine remains the best hope for ending the HIV epidemic.

To combat HIV, we now have at our disposal new information about the molecular and immunologic basis of disease and improved tools for analysis of virus structure and measurement of immune responses. This scientific knowledge forms the basis for new ideas that could lead to novel strategies for effective vaccination. In addition, the scientific and industrial infrastructure has advanced to facilitate production and evaluation of vaccines. Nonetheless, the process of moving vaccine concepts through preclinical development and into initial clinical trials can be slow and

unpredictable. Years of investment and research are required to progress through initial vaccine research, preclinical testing, and development to achieve an effective vaccine. In this setting, VRC has a unique opportunity and responsibility to facilitate the transition of new concepts in microbial pathogenesis, mechanisms of immunity, and vaccine design into clinical applications.

HIV strains worldwide display tremendous genetic diversity that may limit the protective immunity elicited by a single vaccine. Two types of HIV can be distinguished: these have been termed HIV-1 and HIV-2. HIV-2 is endemic in West Africa but is rare outside the region, while HIV-1 is the cause of the global pandemic. HIV-1 is classified into distinct genetic subtypes, or clades. For reasons that are not clear, these subtypes have distinct geographic distributions. To be effective, an HIV vaccine, or vaccines, will have to elicit immune responses against diverse strains of HIV-1. Also, because HIV attacks the primary cells of the immune system, persistent infection fails to produce effective immunity in a large percentage of the population. We are just beginning to understand how the virus evades immunologic surveillance to cause persistent infection and disease.

Development of an effective vaccine against HIV is the primary mission of VRC. To this end, VRC collaborates closely with the NIAID Division of AIDS (DAIDS), particularly with regard to regulatory support and implementation of clinical trials through established trial networks. In addition to its research program for HIV/AIDS, VRC's research programs in biodefense have been expanded, intensified, and accelerated. For example, VRC, working closely with the NIAID Division of Microbiology and Infectious Diseases (DMID) and with industry partners, is positioned to make substantive contributions in the development of vaccines protecting against Category A and B agents such as smallpox, West Nile virus, and hemorrhagic fever viruses (such as Ebola) posing a potential bioterrorist threat.

VRC also is collaborating closely with DMID and the NIAID Division of Intramural Research to develop a vaccine for severe acute respiratory syndrome (SARS).

Scientific Areas of Focus

Historically, the process of vaccine development can be characterized as empiric, guided more by trial and error with inactivated or attenuated organisms than by rational design that builds on basic concepts in immunology and virology. Although this development process has been successful to combat numerous important infectious agents, many diseases remain for which no vaccine exists. A new science of vaccinology that takes advantage of the latest technologies and scientific knowledge to design effective vaccine strategies is now emerging. This process of rational vaccine design is closely coordinated with evaluation of vaccine candidates in animal models and human clinical trials. The VRC strategic plan is predicated on the belief that development of an effective AIDS vaccine will benefit from a thorough understanding of the basis of protective immunity to the virus and the mechanisms by which HIV evades immune surveillance. By having diverse components of vaccine research, development, production, and evaluation readily accessible at one site, along with a group of committed investigators with diverse skills but a common goal, VRC has embarked on a comprehensive and systematic approach to vaccine development.

The VRC process of rational vaccine design is closely coordinated with evaluation of vaccine candidates in animal models and human clinical trials. By embracing new discoveries and using them for the rational design of experimental vaccines, an iterative process of vaccine development, in which clinical evaluation informs basic research, is being established. The science of vaccinology is by its nature interdisciplinary, combining basic and applied research in immunology, virology, disease pathogenesis,

molecular biology, and structural biology with clinical trials methodology. By encompassing these activities at a single center possessing the capacity for vaccine production, VRC hopes to advance the science of vaccine development.

The same infrastructure being employed to develop an effective HIV vaccine also is being deployed in the search for an improved smallpox vaccine and for effective vaccines against Ebola, West Nile virus, and SARS.

Research Goals and Objectives

VRC has four broadly encompassing research goals, each of which has multiple subparts. The goals are as follows:

- Goal 1: Scientifically design and develop effective vaccine candidates.
 - Use knowledge of the HIV envelope structure to design immunogens that elicit potent virus-neutralizing antibodies through a program of rational structure-based design and screening of immunogens.
 - Develop and optimize gene-based vaccine platforms that elicit broad and potent cell-mediated and humoral immunity.
 - Use state-of-the-art methods in genomics and bioinformatics to advance vaccine development.
- Goal 2: Evaluate and optimize the immune response generated by candidate vaccines.
 - Identify and develop validated, reproducible methods to quantitate vaccine-induced immune responses in humans and primates.
 - Identify vaccine candidates and immunization strategies that enhance

potency, antigen presentation, and immunogenicity.

- Develop rational use of the primate model to assess vaccine strategies and define immune correlates.
- Goal 3: Advance the most promising vaccine candidates into human clinical trials.
 - Develop the infrastructure to produce and test vaccine products.
 - Conduct clinical evaluation of candidate vaccines.
 - Evaluate preventive vaccine candidates in clinical protocols of therapeutic immunization.
- Goal 4: Create the necessary infrastructure for translating basic research to the clinical setting.
 - Establish a contractor-leased and operated Vaccine Pilot Plant (VPP) as a high priority for VRC. VPP will manage production of multiple vaccine candidates originating from VRC. To achieve this objective, VPP will provide research and development services to the Vaccine Production Laboratory located on the Bethesda campus to assist in transferring new vaccine technology for pilot-scale production of clinical trial material. VPP is being designed as a leased pilot plant in Frederick, Maryland, with an anticipated completion date of late 2005. At completion, the VPP will be a self-contained facility of 126,900 square feet with the capacity to produce 4 to 8 clinical lots of vaccine annually. Vaccines produced at the VPP will support phase I and II clinical trials. In addition, the facility will incorporate design features that will allow conversion to larger scale

operations capable of supporting phase III trials, if necessary.

Basic Research

Acquired Immunodeficiency Syndrome

VRC aims to develop vaccine candidates that will induce effective humoral responses (immune protection offered by antibodies) and cellular immune responses (immune protection offered by direct action of immune system cells). Data from several animal model systems strongly suggest that both humoral and cellular immunity play key roles in protection against HIV infection and disease. Based on the assumption that both cellular and humoral immunity are factors in preventing HIV infection or controlling HIV disease, the VRC preclinical research program explores basic science questions relevant to vaccine design. Guided by continuing research that reveals a better understanding of the basic elements of protective immunity, scientists at VRC apply this knowledge toward the design of vaccines.

The VRC program in virus structural biology explores the rational design of vaccines that can induce potent virus-neutralizing antibodies. Using innovative crystallographic techniques, the structure of gp120, an important viral protein on HIV's surface, has been determined at the atomic level, leading to the identification and visualization of numerous overlapping mechanisms of immune evasion. VRC is using this and other structure-based analyses and protein-based principles to assist in the rational development of novel candidate vaccines for HIV. This approach also is being applied to the development of vaccines against other pathogenic viruses of public concern.

Development of candidate vaccines focuses on using portions of engineered HIV genes to express specific HIV proteins capable of triggering a protective immune response. These genes can be delivered using immunization

with either DNA or viral vectors. In DNA immunization, the host is immunized by direct administration of viral genes. Viral vectors also can be constructed. These viral vectors transport one or more HIV genes and cause infected cells to produce HIV-specific proteins. Rodent and primate models can be used to evaluate safety, immunogenicity (induction of immune response), and degree of protection provided by these candidate vaccines. Such preclinical animal testing is closely integrated with VRC's basic science programs to provide information for iterative improvements in the development of new candidate vaccines.

A second major goal of the VRC basic research program is the evaluation and optimization of the immune response generated by candidate vaccines. The development of immunogens (substances causing an immune response) that elicit protective immunity against HIV is guided by studies that systematically evaluate the humoral and cellular immune responses generated by vaccine candidates. The development of reproducible, validated assays to measure T cell function and virus particle reduction is key to successful evaluation of both animal studies and human clinical trials. The VRC Immunology Core is currently designing, optimizing, and performing immunologic assays that measure the two major types of immune responses—cellular and humoral. Candidate vaccines are being evaluated by intracellular cytokine staining, ELISPOT assays, and measurements of neutralizing and binding antibodies. VRC also is expanding current assays to be applicable to more antigens and various clades of HIV as well as exploring ways to optimize and automate assay performance using state-of-the-art technologies in robotics.

Using these newly developing technologies, scientists can determine how effectively a candidate vaccine protects against infection or disease.

Ongoing preclinical studies in small animals and primates are evaluating vaccine dose, formulation, and delivery route and addressing the immunogenicity of multigene vectors and vaccine combinations. The accumulated knowledge from these preclinical studies will be used to develop vaccination strategies that induce optimal immune responses. Preclinical animal testing will be integrated closely with VRC basic science and clinical programs to provide information on the advancement of promising candidate vaccines into human trials.

The gene product Murr1 restricts HIV-1 replication in resting CD4+ lymphocytes.

The human immunodeficiency-1 (HIV-1) virus replicates poorly in resting T cells. Factors that block viral replication in these cells might help to prolong the asymptomatic phase of HIV infection. NIAID scientists have identified and characterized a protein, Murr1, which is involved in the regulation of NFκB and HIV-1 infection. Murr1 acts as a genetic restriction factor that inhibits HIV-1 replication in lymphocytes, which could contribute to the regulation of asymptomatic HIV infection and the progression of AIDS. Research is ongoing to understand the role of Murr1 in HIV-1 infection and to define pathways of molecular regulation of HIV-1. This will help identify targets through which anti-viral drugs may delay the progression of HIV-1 infection to AIDS. Such an understanding will be useful in the development of drugs that can help in the treatment of AIDS, as well as of other viruses, such as Ebola, dengue, and cytomegalovirus.

Scientists identify strategies for human antibodies to overcome HIV-1 defense mechanisms.

HIV-1 utilizes a variety of defense mechanisms to evade the immune system, which poses a significant challenge to the development of an effective vaccine. The immune system produces antibodies against foreign molecules such as HIV. The primary target of antibody recognition is gp120, a protein on the envelope

surface of the virus. Using various structural analyses, scientists have identified two novel mechanisms that allow antibodies to overcome HIV-1's defenses and enhance recognition of the virus. Selection and usage of a gene called V_H and addition of a sulfate molecule to part of the gp120 protein have been demonstrated to enhance antibody recognition, therefore providing new targets for HIV-1 vaccines and therapeutics.

Ebola and Other Viral Hemorrhagic Fevers

Outbreaks of Ebola in Africa kill up to 90 percent of those infected. No effective treatment exists for this highly infectious disease, which causes extensive internal bleeding and rapid death. According to experts, vaccination is the best strategy for preventing or containing this deadly infection. Investigators at VRC, with scientific collaborators at the U.S. Army Medical Research Institute of Infectious Diseases, have developed a potentially effective vaccine strategy for Ebola virus infection in nonhuman primates. Previous VRC studies have shown that a combination of DNA vaccination and boosting with adenoviral (ADV) vectors that encode viral proteins was protective against Ebola viral challenge and generated cellular and humoral immunity in cynomolgus macaques.

West Nile Virus

The NIAID Vaccine Research Center is currently conducting preclinical testing of a West Nile virus vaccine. The VRC proposes to use an existing codon-modified gene-based DNA plasmid vaccine platform to make DNA constructs that express West Nile virus proteins. These vaccine constructs are currently undergoing immunogenicity and viral challenge studies in rabbits. The VRC in collaboration with Vical, Inc. has completed GMP production of the vaccine for a phase I trial scheduled for early 2005.

SARS

In response to the recent global outbreak of SARS (Severe Acute Respiratory Syndrome),

VRC Investigators quickly began working on the development of a potential vaccine. A Cooperative Research and Development Agreement and contract have been established with GenVec, Inc. GenVec is producing preclinical and clinical grade adenoviral vectors that express several SARS proteins. The VRC plans to evaluate the immunogenicity of these vectors preclinically, and will continue to develop and test adenovector-based vaccine candidates against SARS that are suitable for rapid advancement toward clinical trials. In addition, the VRC has contracted with Vical, Inc., to manufacture a SARS DNA-based vaccine encoding the spike (S) glycoprotein of the SARS coronavirus. Recent studies have demonstrated that this vaccine induces T cell and neutralizing antibody responses, as well as protective immunity, in a mouse model. A phase I trial of this recombinant DNA vaccine developed at the VRC is being planned for late 2004 or early 2005.

Clinical and Regulatory Infrastructure

VRC has assembled a full clinical research support team consisting of physicians, study coordinators, nurse practitioners, research nurses, and recruitment and outreach specialists. These staff represent VRC at community events, screen potential volunteers, and perform vaccinations and subsequent follow-up and testing of enrolled volunteers. VRC also has developed the strong regulatory infrastructure required to support the development and testing of vaccines. In collaboration with DAIDS and DMID, VRC staff members manage the submission of Investigational New Drug (IND) applications to the Food and Drug Administration (FDA), develop protocols for human clinical trials, and ensure that all studies are performed in accordance with FDA guidelines, while meeting all applicable reporting requirements.

Human Clinical Trials

A systematic, well-coordinated process of human vaccine trials is essential to effectively develop new vaccines. Although animal models are invaluable for guiding the development of vaccine approaches in general and are indispensable for evaluating efficacy and immune correlates of protection, parallel phase I and II studies in humans are required to validate safety and immunogenicity findings, and only human phase III efficacy trials can determine vaccine efficacy. To efficiently move vaccine development forward, VRC combines traditional empirical vaccine development with hypothesis-driven basic and preclinical research. This approach promotes an iterative process in which data from clinical evaluation will inform basic research and vaccine design, and findings in animal models will help prioritize approaches to test in clinical trials. In addition to traditional phase I studies in HIV seronegative volunteers, VRC has been studying the ability of vaccine candidates to augment native immunity in HIV-infected patients. Intensive evaluation of CD4 and CD8 immune responses will be correlated with control of viral replication and disease progression. In addition to the potential benefit to patients, studies of vaccine therapy will clarify mechanisms of cellular immunity and T cell memory that play a role in protection against HIV. Such data then can be applied to the development of therapeutic and preventive vaccines.

VRC actively collaborates with both intramural and extramural scientists and facilitates the movement of ideas from the broader community into clinical trials. Close ties are maintained with extramural investigators in the HIV Vaccine Trials Network (HVTN), where the infrastructure for conducting larger scale trials already is established. This collaboration will include efforts to develop vaccine candidates that can be evaluated at international field sites. When products emerge with real promise for licensure, VRC also will interact with the pharmaceutical

industry, in which there is a large capacity for and experience in product development and distribution. Therefore, VRC is working to fill the gap between new basic concepts in immunology and initiation of clinical trials by applying state-of-the-art methods to rational vaccine design and evaluation at a single site.

Acquired Immunodeficiency Syndrome

In November 2002, the VRC launched a phase I clinical study of a novel DNA vaccine directed at the three most globally important HIV subtypes, or clades. The vaccine, developed by the VRC, incorporates HIV genetic material from clades A, B, and C, which cause about 90 percent of all HIV infections around the world. This is the first multigene, multiclade HIV vaccine to enter human trials and marks an important milestone in the search for a single vaccine that targets U.S. subtypes of HIV as well as clades causing the global epidemic. The first phase of the trial is being conducted by the VRC at the National Institutes of Health in Bethesda, MD, and is designed to determine the vaccine's safety at 3 dose levels. All 50 healthy, HIV-negative volunteers have completed clinical follow up and the study has recently been unblinded. A larger clinical trial to further evaluate safety, immune response, and schedule is being conducted through the DAIDS, HVTN at several domestic sites, and a phase I clinical trial with 30 healthy volunteers will also be carried out in Uganda as a collaboration between the Makerere University–Walter Reed Project, DAIDS, and the VRC. The DAIDS' Adult AIDS Clinical Trials Group is also conducting a phase I clinical trial of this vaccine in HIV-infected volunteers.

The VRC has initiated a phase I clinical trial of a novel adenoviral HIV multiclade vaccine. The VRC eventually plans to combine DNA and adenoviral vector technologies into a prime-boost strategy for HIV vaccine development.

Ebola

In November 2003, the VRC initiated the first human trial of a vaccine designed to prevent Ebola infection. The trial is currently fully enrolled and to date, the injections have been well tolerated. In addition to testing preventive vaccine candidates, the VRC is currently developing a vaccine that might be useful in an acute outbreak setting. For example, a recently tested candidate (a single vector ADV-only) vaccine elicited protective immunity in monkeys after a 4-week postvaccination challenge, in contrast to previous 10-week or 6-month vaccine regimens. A second-generation product that would provide coverage for Marburg and possibly Lassa virus may also be evaluated.

MVA

VRC currently is testing modified vaccinia Ankara (MVA) as an attenuated poxvirus with the potential to protect against vaccinia (the virus used to vaccinate against smallpox) or variola (the virus that causes smallpox). The vaccine was provided by Therion Biologics Corporation as part of a collaboration with VRC and DMID. Two phase I clinical trials are now underway testing MVA as a component of a safer smallpox vaccine in both vaccinia-naïve and vaccinia-immune populations. Scientific collaborations have been developed with both DMID and private-sector partners for the development and production of MVA as a component of a safer smallpox vaccine for further clinical testing. Following the completion of the current phase I trials, further development of MVA as a component of a safer smallpox vaccine will be directed by DMID.

New Initiatives

VRC is planning new initiatives to support the growing needs of its expanding mission. VRC currently conducts phase I vaccine studies on the NIH Bethesda campus. In preparation for the conduct of phase II and III studies and to manage the complex activities related to international vaccine development, VRC has created a team dedicated to advanced clinical development of candidate vaccines.

To further support research and development on vaccines for smallpox, Ebola, and West Nile virus, an additional laboratory dedicated to biodefense research is currently being formed, with the purpose of accelerating both basic research and subsequent development of biodefense-related vaccines.

Human Clinical Trials and Licensure of an AIDS Vaccine

VRC is working closely with its scientific collaborators and with FDA to discuss the potential for expedited approval of AIDS vaccines. The carefully considered use of surrogate end points (i.e., measures of the vaccine's ability to provoke an immune response) in AIDS vaccine trials could substantially accelerate the licensure of an effective AIDS vaccine. Clinical information validating the use of surrogate end points can accrue from well-designed trials, and this information can be applied to the design of future trials.

¹ UNAIDS. AIDS epidemic update: 2004. Available at <http://unaids.org/wad2004/report.html>

DIVISION OF EXTRAMURAL ACTIVITIES

Mission

The Division of Extramural Activities (DEA) (www.niaid.nih.gov/ncn) serves NIAID's extramural research community and the Institute in several key areas: overseeing policy and management for grants and contracts, managing NIAID's research training and international programs, and conducting initial peer review for funding mechanisms with Institute-specific needs.

In addition to providing broad policy guidance to Institute management, DEA also oversees NIAID's chartered committees, including the National Advisory Allergy and Infectious Diseases Council (NAAIDC); disseminates information to its extramural community through its large Internet site; and conducts extramural staff training and communications through the NIAID intranet.

DEA staff members interact intensively with grantees, contractors, reviewers, NAAIDC members, applicants, and staff of the other NIAID extramural divisions—the Division of Acquired Immunodeficiency Syndrome; the Division of Allergy, Immunology, and Transplantation; and the Division of Microbiology and Infectious Diseases.

DEA's Grants Management Branch (GMB) issues all NIAID grant awards after negotiating the terms of the award with grantees. GMB specialists determine award amounts, develop administrative terms and conditions, and release official award documents. They help clarify grant policies and procedures for investigators and answer their business and administrative questions, such as what costs are allowed and how to formulate a budget for an application. GMB specialists supervise the day-to-day administration and financial management of

Institute grants and cooperative agreements, while ensuring that grants comply with existing policies.

The Contract Management Program (CMP) (www.niaid.nih.gov/contract) manages the administrative aspects of NIAID's research and development contract portfolio. CMP specialists help develop requests for proposals, negotiate technical and business aspects of proposals, and select proposals for funding. Contract specialists are well-versed in legal, technical, business, and cost-related topics, including Federal Acquisition Regulations. They provide investigators with guidance on changes in the scope of the research, the use of funds, and other administrative issues.

The Scientific Review Program (SRP) conducts peer review of NIAID's contract proposals and grant applications that address Institute-specific needs. These typically include program projects (P), cooperative agreements (U), training (T), and research career (K) grants, as well as applications responding to requests for applications (RFAs) and requests for proposals (RFPs). Scientific review administrators assist NIAID staff members with the design, development, and review of initiatives. They also conduct initiative phasing, perform quality control of RFAs and RFPs, and formulate peer review strategies.

The Referral and Program Analysis Branch (RPAB) handles receipt and referral for grant applications that undergo initial review at NIAID. RPAB also performs scientific classification and data analysis of NIAID's funded grants, contracts, and intramural research projects for official science-information reports.

Several offices and staff members in DEA's Office of the Director (OD) play specialized roles for the extramural community and the Institute. DEA staff members are a focal point for facilitating and coordinating several key activities, including innovative electronic systems. In addition, the OD is a long-time leader in developing

innovative technologies that have been adopted by the NIH, including electronic peer review and acquisition systems.

- The Office of Special Populations and Research Training (OSPRT) (www.niaid.nih.gov/facts/mwhhp.htm) manages and awards fellowships (F), institutional training (T), and research career (K) grants. OSPRT provides oversight and coordination for NIAID's minority and women's health activities and initiatives and manages research supplements for underrepresented minorities and scientists with disabilities.
- The Office for Innovation and Special Programs manages grants for NIAID's small business programs—Small Business Innovation Research and Small Business Technology Transfer.
- The Office of International Extramural Activities (www.niaid.nih.gov/ncn/grants/int/default.htm) helps develop policies for international applicants and grantees. It reviews the financial systems of non-U.S. grantees and communicates with other Federal agencies about international policies for select agents.
- The Office of Knowledge Resources (OKR) informs the Institute and its extramural research community of funding opportunities, advice, policy updates, and other news. OKR provides budget and payline information as well as tutorials on NIH operations, planning and writing grant applications, and managing grant awards. The *NIAID Funding* newsletter and NIAID Funding Web site (www.niaid.nih.gov/ncn) are designed for the extramural research community, while the *NIAID Insider* newsletter and the *Inside Extramural* intranet (intra.niaid.nih.gov/organization/dea) are tailored to Institute staff.
- The Committee Management Office oversees the legal and policy requirements for NIAID's chartered committees, which include the NAAIDC, the Board of Scientific Counselors, the AIDS Research Advisory Committee, and special emphasis panels. It also administers Scientific Review and Evaluation Awards.
- The Office of Data Quality and Initiative Development initiates, plans, designs, and oversees extramural research initiatives. It also performs review and quality control of solicited grant and contract initiatives.
- The Office of Scientific Resource Development (OSRD) develops Web-based and classroom training for NIAID staff and expands Institute learning resources. It educates NIAID staff on key scientific, clinical, and management mechanisms to enhance job performance.
- The Office of Program Coordination and Operations manages NIAID initiative phasing plans, develops NIAID Council guidance and timetables, manages the grants records center, and works with the administrative office to manage daily functional activities.

SELECTED SCIENTIFIC AREAS OF RESEARCH

ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS)

Significant progress has been made since 1981, when mysterious cases of pneumonia led researchers to identify the disease known as AIDS. Research has led to a better understanding of the structure of human immunodeficiency virus (HIV), which causes AIDS, how HIV attacks the immune system, the role of the immune system in controlling HIV infection, and how to intervene therapeutically. Potent therapeutic regimens, commonly referred to as highly active antiretroviral therapy, or HAART, have been successful in suppressing HIV to virtually undetectable levels in the blood and decreasing the incidence of opportunistic infections. HAART has greatly improved the quality of life of many HIV-infected people worldwide and has led to a dramatic decline in AIDS-related deaths.

Despite these scientific advances, the HIV/AIDS pandemic continues to rage around the world, with an estimated 39 million people living with the disease. In 2004, 3.1 million people died from AIDS, and 4.9 million people were newly infected with HIV. Of the 4.9 million new infections, 640,000 were in children. Globally, just under half of all people living with HIV are female. An estimated 40,000 people have been infected with HIV each year in the United States in the past 10 years, but the epidemic is now disproportionately lodged among African Americans and is affecting much greater numbers of women¹.

Since the beginning of the epidemic, NIAID's comprehensive research program has been at the forefront in the fight against HIV/AIDS. NIAID supports a broad array of domestic and international HIV/AIDS research programs and collaborates with more than 40 countries through investigator-initiated research grants and multicenter prevention, vaccine, and therapeutic research networks. (See Division of AIDS Overview on page 11 for a description of

programs.) With a growing number of research programs and initiatives, NIAID is poised to tackle new global research challenges as well as the changing demographics of the HIV/AIDS epidemic.

Basic Research

Basic research in HIV pathogenesis, microbiology, immunology, virology, and animal model development lays the foundation for advancing research in HIV treatment and prevention. At NIAID, this research is conducted primarily through investigator-initiated research as well as a number of targeted programs and several large cohort studies.

This past year, as a result of advances in basic science, researchers have learned how virion infectivity factor (Vif) of HIV may counteract the effects of APOBEC3G, a novel antiviral protein in normal human cells that causes lethal mutations in HIV and other retroviruses. The ability of Vif to counteract the antiviral activity of APOBEC3G by targeting it for destruction helps explain Vif's importance in viral replication. Thus, interventions that either modulate levels of APOBEC3G or block its interaction with Vif are potential new targets for therapeutic interventions against HIV.

NIAID-funded investigators also found that efficient budding of HIV requires binding between a specific portion of the HIV coat and a human cellular protein called TSG101. This human protein is normally complexed with ESCRT-I and both are important components in the cell's machinery for assembling protein complexes in vesicles that transport proteins out of the cell. This discovery helps explain HIV budding and infectivity, providing new avenues for the development of drugs to inhibit HIV replication.

Several studies from the Multicenter AIDS Cohort Study (MACS) found that GB virus type C (GBV-C), a flavivirus that does not

induce disease in humans, prolongs survival of HIV-infected patients. A NIAID-supported investigator found that specific chemokine levels (RANTES, MIP-1 α , MIP-1 β and SDF-1) were consistently higher in GBV-C-infected peripheral blood mononuclear cells. This discovery helps explain the protective effect of GBV-C infection in HIV-positive persons.

A NIAID-funded research team identified a protein that blocks HIV replication in monkey cells. The protein, TRIM5- α , is the first identified to specifically target HIV's coat or capsid and inhibit viral uncoating, which is essential for the virus to reproduce. Identification of this HIV-blocking factor opens new avenues for intervening in the early stage of HIV infection, before the virus can gain a toehold, while providing insights about viral uncoating, which is a step in the viral life cycle that is not well understood and could help lead to future improvements in therapies for HIV disease.

Although much has been learned, questions still remain about (1) how HIV establishes and

maintains persistent latency, (2) how HIV evades the antiviral mechanisms of the immune system, (3) the components and steps in HIV budding, (4) the protective effect of GBV-C infection in HIV infected individuals, and (5) HIV blocking factors that disrupt viral uncoating. Answering basic scientific questions about how the virus attacks the body and how the body defends itself is critical to providing additional potential targets against which therapeutic interventions and vaccines can be directed.

Vaccine Research

An HIV vaccine that is simple to administer, inexpensive, and induces long-lasting immunity against all HIV subtypes is critical to the effective control of the global spread of HIV. It is, therefore, one of NIAID's highest priorities, albeit one of the most difficult challenges in HIV/AIDS research. NIAID supports a spectrum of HIV vaccine research and development activities, including basic research (discovery), preclinical screening and animal model development, product development and manufacturing, and clinical research. The scope and breadth of these programs and resources continue to significantly advance global HIV vaccine development efforts.

Over the years, NIAID-supported HIV vaccine research has led to the identification of new and innovative HIV vaccine designs, improvements in vaccine delivery, development of innovative laboratory techniques and animal models for evaluating vaccines, and evaluation of over 40 vaccine candidates in clinical studies. Additional studies have already been initiated or are being planned to evaluate the safety and immunogenicity of a number of new candidate vaccines, including lipopeptide vaccines alone and in combination with a canary pox vaccine, a Venezuelan equine encephalitis replicon vector vaccine, novel DNA vaccines, a recombinant nonreplicating adenovirus vaccine, modified vaccinia Ankara and other novel pox vector-based vaccines, a cytotoxic T lymphocytes multi-epitope peptide vaccine, and molecular adjuvants.



Demonstration of vaccination procedure on uninfected volunteer participating in a clinical trial.

In addition, NIAID's HIV Vaccine Trials Network (HVTN), established to evaluate candidate vaccines worldwide, has been expanded to meet the demands of the growing number of candidate vaccines currently in the pipeline for which large efficacy trials may be needed. In collaboration with Merck, NIAID's HVTN is currently planning a phase IIb HIV vaccine trial to evaluate the ability of MRKAd5 HIV-1 gag/pol/nef, an adenovirus-based vaccine, to prevent infection or delay HIV disease in 1,500 high-risk volunteers. The study began enrolling volunteers at the end of calendar year 2004 in the United States, the Caribbean, South America, and Australia. Since rapidly identifying a safe and effective HIV/AIDS vaccine requires unprecedented cooperation among private sector vaccine developers, academic researchers, nonprofit organizations, and affected communities throughout the world, NIAID has established a number of collaborations and partnerships, including partnerships with other government such as the U.S. Army Medical Research and Materiel Command of the Department of Defense and non-governmental agencies. Prominently, NIAID has forged a new, innovative collaboration called the Partnership for HIV/AIDS Vaccine Evaluation (PAVE), which includes the HIV vaccine program of the Centers for Disease Control and Prevention, the U.S. Military HIV Research Program, and several nongovernmental organizations active in HIV vaccine development. PAVE will accelerate the global HIV vaccine research effort. It will also help ensure coordination and efficiency among U.S. Government agencies and their partners. These partnerships are particularly important in the conduct of research in resource-poor developing countries, which are hardest hit by the epidemic. In addition, NIAID is helping to develop Global HIV Vaccine Enterprise, an alliance of independent organizations formed to accelerate HIV vaccine development and evaluation through a shared strategic scientific plan that is implemented in a transparent, coordinated, and collaborative manner. (See the

Vaccine Research and Development section on page 126 for additional vaccine information.)

Nonvaccine Prevention Research

To control the HIV/AIDS pandemic, new and more effective methods and strategies are needed to prevent HIV infection. Until a highly efficacious vaccine is developed, control of the pandemic will still require a combination of prevention approaches. NIAID's HIV Prevention Trials Network (HPTN) develops and tests promising nonvaccine strategies to prevent the spread of HIV/AIDS, including:

- Drugs or vaccines that are practical and easy to use to prevent mother-to-child transmission (MTCT) of HIV, including prevention during breastfeeding;
- Microbicides to prevent sexual transmission of HIV;
- Antiretroviral therapy (ART) that may reduce the spread of HIV from infected persons to their sexual partners;
- Measures to control other sexually transmitted diseases and thereby decrease the risk of co-infection with HIV;
- Interventions to reduce behavior that exposes people to HIV; and
- Programs to curb the spread of HIV by reducing intravenous drug use.

NIAID-funded research that makes use of the HPTN has led to important scientific advances that increase our understanding about the transmission of HIV. These findings provide a foundation for developing and testing innovative prevention strategies.

Notably, Project EXPLORE, which was an NIAID-funded, national HIV behavioral prevention trial involving nearly 4,300 men who have sex with men (MSM), reported a 20.5 percent reduction in sexual intercourse with HIV-

positive and HIV status-unknown individuals, when the experimental behavioral intervention was compared to standard individual counseling. Although the study did not find a statistical reduction in HIV infection, it underscores the need for other behavioral studies. Project EXPLORE is one of the largest behavioral studies of its kind and was designed to examine whether an intensified program of counseling on high-risk behavior helps to prevent MSM from acquiring HIV.

Prevention research involving topical microbicides is described in the Sexually Transmitted Infections section on page 114.

Therapeutics

One of the primary goals of HIV/AIDS therapeutic research is to evaluate innovative therapeutic strategies for HIV/AIDS and the complications and co-infections in all stages of HIV infection. As a result of HAART, the life expectancy of HIV-infected individuals has dramatically increased. As the number of individuals living with HIV disease increases, many develop a host of complications resulting from their therapeutic regimens, including the development of drug resistance and metabolic abnormalities and toxicities. Moreover, the immune system only partially recovers during HAART treatment. Thus, new therapies and ways to expand the clinical benefit of currently approved therapies are still urgently needed. NIAID's therapeutics research programs and networks are focusing on these issues.

In addition to a comprehensive clinical research agenda in the United States, NIAID fosters the study of therapy for HIV and accompanying opportunistic infections (OIs) internationally, including research in resource-poor developing countries. Key issues to be addressed in these countries include: therapeutic regimens suitable for resource-poor settings; when to start therapy; how to monitor safety and efficacy with minimal laboratory resources; interactions of endemic

infections and HIV; and drug interactions, including the drugs used to treat endemic infections. Efforts are being undertaken to provide training in HIV disease and treatment for local healthcare workers in developing countries, as well as reciprocal training (or twinning) for U.S. research collaborators in the healthcare needs of developing countries. This is being accomplished through a variety of mechanisms, including the expansion of existing clinical trials groups to collaborate with investigators in developing countries, direct funding of investigator-initiated research through R01 awards, and the development of comprehensive HIV research centers through the Comprehensive International Program of Research on AIDS.

The majority of NIAID's therapeutic clinical trials are conducted through the Adult AIDS Clinical Trials Group, the Pediatric AIDS Clinical Trial Group, and the Terry Beirn Community Programs for Clinical Research on AIDS. These networks conduct, at any given time, over 100 clinical trials addressing a full range of AIDS and AIDS-related infections, complications, and co-infections. Examples of these studies include hepatitis C virus (HCV) co-infection, metabolic complications of HAART, OIs, treatment-naïve patients, salvage therapy, women-specific studies, and MTCT.

NIAID is currently implementing ACTG 5175, a large international clinical trial to evaluate the efficacy of protease inhibitors and non-nucleoside reverse transcriptase inhibitors containing therapy combinations for initial treatment of HIV-infected individuals from diverse areas of the world. In addition, NIAID continues to support two large multicenter studies, the Strategies for Management of Anti-Retroviral Therapy (SMART) study (www.smart-trial.org) and Evaluation of Subcutaneous Proleukin in a Randomized Interventions (ESPRIT) (www.niaid.nih.gov/dir/labs/lir/hiv/esprit.htm). NIAID also has several studies under way that address the timing and sequence of treatment of HIV and tuberculosis co-infection, as well as the

management and treatment of hepatitis B virus (HBV) and HCV co-infection with HIV. One such study is a phase II long-term maintenance therapy trial designed to study whether long-term maintenance with pegylated-interferon (PEG-IFN) reduces the rate of disease progression in subjects with HCV/HIV co-infection who did not respond to the standard treatment regimen of PEG-IFN plus ribavirin. Another trial is evaluating the ability of two anti-HBV drugs to control HBV infection without causing drug resistance, which is a common occurrence with chronic use of lamivudine for treating HBV infection.

NIAID continues to expand MTCT research studies internationally. Maintaining Options for Mothers Study is a prospective, randomized clinical trial evaluating the effectiveness of three different antiretroviral regimens for the prevention of nevirapine (NVP) resistance after single-dose NVP has been administered during delivery. Another important study, Optimal Combined Therapy after NVP Exposure is a phase III study that compares the response of two different classes of antiretroviral drugs in women who have received only a single dose of NVP.

NIAID also continues to evaluate new classes of antiretroviral compounds, including entry inhibitors, which show increasing promise in preclinical and clinical studies. Building on the success of the fusion inhibitor, Fuzeon, NIAID is conducting studies focused on developing an orally available drug that will fight HIV at the point of entry.

A major goal of NIAID intramural researchers and their collaborators is to discover new therapies for AIDS that are less expensive or less toxic than current therapies and can therefore be used more widely. Several such new approaches are under study in NIAID's Division of Intramural Research (DIR). For some HIV-infected patients whose plasma levels of virus have fallen to undetectable levels while on HAART, it may prove feasible to move from

a continuous HAART regimen to intermittent therapy in which an individual discontinues, and then resumes, HAART in a preplanned cyclic fashion. This cyclic approach to treatment, known as structured intermittent therapy, might enable an HIV-infected person to have regular HAART-free periods while maintaining a minimal viral load and adequate levels of CD4+ T cells.

To test this concept, DIR researchers and their collaborators investigated whether short-cycle intermittent therapy consisting of cycles of a once-daily regimen of two nucleoside reverse transcriptase inhibitors—didanosine, lamivudine—and one non-nucleoside reverse transcriptase inhibitor—efavirenz—for one week, followed by a week off therapy, had a beneficial effect on patients with chronic HIV infection. Seven of 8 patients evaluated maintained suppression of plasma HIV RNA for 60–84 weeks (30–42 cycles) while preserving CD4+ T-cell counts. In addition, there was no evidence for the emergence of drug resistance to antiretroviral drugs.² It is important to note that the need for strict adherence to this type of regimen is necessary, and the feasibility of this approach awaits the results of randomized, controlled clinical trials underway in the United States and Africa. If safety and efficacy of short-cycle intermittent therapy is ultimately demonstrated in clinical settings, it might prove to be an important strategy to expand therapy in resource-limited settings.

Although HAART has dramatically improved the clinical outcome for many HIV-infected patients, the associated cost, toxicity, and development of drug resistance underscore the need for additional therapeutic strategies. Strategies aimed at enhancing the ability of the immune system to fight HIV infection are currently being investigated by NIAID intramural scientists as potential supplements to ART. These immune-based strategies include treatments that stimulate or suppress a particular part of the immune system, infusion of additional immune

system cells, and therapeutic immunizations. For example, NIAID's long-term basic research into the function of interleukin-2 (IL-2), a protein that stimulates CD4+ T cells to mature and multiply, and clinical studies of its safety and efficacy for HIV therapy have led to promising results. Of note, in a long-term cohort the current average IL-2 cycle frequency required to maintain their CD4+ T cell counts in the elevated range is on the order of only one cycle every 3 to 4 years. These data should lead to a much greater acceptance of intermittent IL-2 therapy as a potential adjunctive treatment in the long-term management of HIV-infected patients.³

Despite the development of successful therapeutic strategies, it has not been possible to eradicate HIV in infected individuals. This is due to the persistence of various viral reservoirs, including replication-competent virus, HIV-1 proviral DNA, and spliced and unspliced HIV-1 RNA in CD4+ T cells. Recent observations by NIAID scientists suggest that strategies aimed at minimizing cellular activation might further diminish residual viral replication in patients receiving HAART. In order to address this question, they have begun a pilot clinical trial to examine the safety and tolerability of a mildly immunosuppressive agent, daclizumab. The study will demonstrate whether daclizumab can normalize immunologic profiles and reduce plasma viremia in study volunteers.

The next generation of antiviral therapeutics may include compounds that prevent HIV from entering CD4+ T cells. NIAID researchers have constructed a compound that inhibits entry of HIV into CD4+ T cells and does not enhance HIV entry under any conditions. This compound is a large protein that binds specifically to the part of HIV that attaches to the CD4+ T cells. The protein exhibited extraordinarily strong binding to HIV, and relatively small amounts were able to neutralize HIV samples from a broad range of infected patients. In addition, the protein activates natural killer (NK) cells, which are an important defense against the virus. The specificity for both the HIV envelope and the NK cell receptor may promote NK cell-mediated killing of HIV-infected cells. Based on these observations, NIAID scientists are evaluating the compound for its potential as both a therapeutic agent and a vaccine adjuvant.

Current NIAID programs that support targeted drug discovery for HIV/AIDS also include: the Novel HIV Therapies: Integrated Preclinical/Clinical Program; the Innovation Grants for AIDS Research Program; the Therapeutics Research on AIDS-Associated Opportunistic Infections and Malignancies Program; the Liver and Pancreatic Disease in HIV Infection Program; the Complications of Antiretroviral Therapy Program; and the International Studies of AIDS-Associated Co-Infections Program.

ANTIMICROBIAL RESISTANCE

Drug-resistant infectious agents—those that are not killed or inhibited by antimicrobial compounds—are an increasingly important public health concern. Antimicrobial resistance has become a significant public health problem because of overuse of antimicrobial drugs and failure to ensure proper diagnosis and adherence to treatment. Serious cases of resistance have occurred in hospitals and communities and include nosocomial (hospital-acquired) respiratory and bloodborne infections. The impact of antimicrobial resistance includes an increase in the cost of treating infections, the need to use a greater number of broader spectrum and more toxic drugs to clear resistant infections, untreatable infections leading to increased morbidity and mortality, and the spread of resistant infectious agents in hospitals and the outside community.

The phenomenon of antimicrobial resistance is prevalent in developed countries and also is a challenge for developing areas of the world. Factors in the global emergence of resistant malaria parasites, diarrheal pathogens, and sexually transmitted bacteria include incomplete or inadequate antimicrobial therapy, ineffective counterfeit drugs, and lack of access to healthcare. These factors are different from those that influence resistance patterns seen domestically. New prevention and treatment strategies are needed, as well as the effective use of the tools currently available for fighting resistant infectious diseases.

Hospitals are a critical component of the antimicrobial resistance problem. Many factors are believed to contribute to the emergence of drug resistance among nosocomial pathogens, including overuse of broad-spectrum agents, increasing numbers of susceptible and immunocompromised patients, use of invasive procedures and devices, and the breakdown of infection- and disease-control practices. Currently 5 to 10 percent of patients admitted to acute care

hospitals acquire healthcare associated infections, and the risks have increased steadily during the recent decades.⁴ Approximately 2 million patients in the United States get an infection as a result of receiving healthcare in a hospital, and overall 70 percent of the bacteria causing such infections are resistant to at least one of the drugs most commonly used to treat these infections.⁵

Antimicrobial resistance also has been shown to negatively affect patient clinical outcome and cost to the healthcare system. Several studies utilizing different methodologies have concluded that methicillin-resistant *Staphylococcus aureus* (MRSA) infections are more frequently fatal than methicillin-sensitive infections. One retrospective cohort analysis revealed a 22 percent difference between mortality in MRSA bacteremia (35.3 percent) compared with methicillin-sensitive bacteria (8.8 percent). Another study, looking at the health and economic impact of vancomycin-resistant enterococci (VRE) infections, showed increases in case fatality rates and hospital costs in the VRE group as compared to matched controls, respectively.⁶

One of the most disturbing trends is the emergence of multidrug-resistant pathogens in the community outside hospitals. MRSA, long a problem in intensive care units (ICUs) and nursing homes, is an emerging community-acquired pathogen among patients without history of hospitalization or previous infections. There are increasing reports of MRSA causing serious skin and soft-tissue infections among athletes, prisoners, persons in daycare settings, and injection drug users.

Streptococcus pneumoniae (pneumococci) causes tens of thousands of cases of meningitis and pneumonia and 7 million cases of ear infection in the United States each year, and multidrug-resistant pneumococci are common and increasing.⁷ Resistance of *S. pneumoniae* to antimicrobial agents continues to be a major public health concern.

An estimated 300 million to 500 million people worldwide are newly infected with the parasites that cause malaria, and an estimated 1 million people die every year from this infection.⁸ Resistance to chloroquine, once widely used and highly effective for preventing and treating malaria, has emerged in most parts of the world. Resistance to other antimalarial drugs also is widespread and growing.

Multidrug-resistant tuberculosis (MDR-TB) is as contagious as drug-susceptible tuberculosis but requires much more extensive and costly therapy. The incidence of MDR-TB has increased dramatically in the past decade, and strains of the tubercle bacillus that are resistant to one or more drugs are now present in all regions of the world.⁹ Accurate and rapid diagnosis of MDR-TB often is not available, resulting in inadequate treatment of patients, who as a result, remain infectious longer and are able to spread MDR-TB to other persons. Because TB is a major cause of death in persons also co-infected with HIV, spread of MDR-TB in this vulnerable population has the potential to dramatically increase the death toll from TB.

Diarrheal diseases cause an estimated 3 million deaths a year—mostly in developing countries where resistant strains of highly pathogenic bacteria, such as *Shigella dysenteriae*, *Salmonella typhimurium*, and *Vibrio cholerae*, are emerging. Eighty percent of *S. dysenteriae* isolates in Bangladesh, for example, have been found to be resistant to ampicillin and trimethoprim-sulfamethoxazole (TMP-SMX), compared with approximately 40 percent of the other *Shigella* species.¹⁰ Also, resistance is increasing to several critical antimicrobials used to treat invasive *Salmonella* infection, including extended-spectrum cephalosporins and quinolones. In resource-poor countries, drug-resistant *Salmonella* infections could eventually become untreatable.¹¹ Finally, a study in Indonesia found *V. cholerae* O1 strains resistant to ampicillin, TMP-SMX, chloramphenicol, and tetracycline; similar results were obtained for non-O1 *V. cholerae* strains.¹²

In response to the increasingly important public health concerns outlined above, NIAID funds a diverse portfolio of grants and contracts to study antimicrobial resistance in major viral, bacterial, fungal, and parasitic pathogens. NIAID-funded projects include basic research into the disease-causing mechanisms of pathogens, host-pathogen interactions, and the molecular mechanisms responsible for drug resistance as well as applied research to develop and evaluate new or improved products for disease diagnosis, intervention, and prevention.

In addition, NIAID supports a number of clinical trial networks with the capacity to assess new antimicrobials and vaccines with relevance to drug-resistant infections. Among these networks are the AIDS Clinical Trials Group, the Collaborative Antiviral Study Group, the Tuberculosis Research Unit, the Vaccine and Treatment Evaluation Units, and the Bacteriology and Mycology Study Group (BAMSG), with one area of emphasis directed toward serious resistant bacterial infections. A study protocol, “Infection-Control Strategies to Reduce Colonization and Infection Caused by Antimicrobial-Resistant Bacteria in Adult ICUs,” is under development and will be conducted through the BAMSG.

In recent years, NIAID has launched several projects to accelerate research on antimicrobial resistance, to develop products to address this challenge, and to support new clinical trial activities in this area. The Network on Antimicrobial Resistance in *Staphylococcus aureus* provides a repository of resistant bacteria, a registry of case information, and a network of investigators to support and stimulate research in the area of resistant bacterial infections. In fiscal year 2002, NIAID announced an initiative called Partnerships for Novel Therapeutics and Vector-Control Strategies in Infectious Diseases, with the goal of supporting partnerships to develop new drugs and diagnostics in areas that are not currently a high priority for industry but are likely to have a high impact on public health. In 2003, NIAID awarded 18 grants under a new

initiative designed to encourage the submission of grant applications on “Innovative Approaches for Combating Antimicrobial Resistance.”

NIAID cochairs the Interagency Task Force on Antimicrobial Resistance with the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration; eight other Government agencies also are represented on the task force. In June 2004, a public meeting was held to discuss progress in implementing “A Public Health Action Plan to Combat Antimicrobial Resistance Part 1: Domestic Issues” and obtain feedback from stakeholders. The Action Plan, which reflects a broad-based consensus of Federal agencies on actions needed to address antimicrobial resistance, is based on input from a wide variety of constituents and collaborators. The Action Plan is available online at CDC’s antimicrobial resistance Web site, www.cdc.gov/drugresistance.

A new research initiative, “Sepsis and CAP: Partnerships for Diagnostics Development,” was announced in August 2004. The purpose of this initiative is to support industry development of broad diagnostic technologies that provide early detection of select major causes of septicemia, bacteremia, candidemia, and community-acquired pneumonia. Also, a protocol for evaluating an anti-endotoxin vaccine for human use is in early phase studies. Preliminary results show that the anti-endotoxin vaccine appeared to be safe and well-tolerated in humans. Studies to further evaluate safety, functional activity, and immunogenicity are underway.

NIAID also investigates antimicrobial resistance in its Division of Intramural Research (DIR). In laboratory and clinical studies, DIR scientists study the microbe and the host to elucidate factors contributing to resistance to a variety of antimicrobial drugs. For example, to respond to the growing threat to TB-control programs posed by the emergence of MDR-TB, DIR scientists are studying the development of resistance to specific anti-TB drugs (such as pyrazinamide and

isoniazid) as well as the larger issue of whether specific factors exist that predispose some patients to develop multiple drug resistance. These scientists, in collaboration with South African colleagues, recently identified the key role played by an unusual DNA polymerase enzyme in the generation of the genetic mutations that confer drug resistance in *Mycobacterium tuberculosis*. This finding may lead to the development of anti-TB drugs that target this enzyme.¹³

In addition, intramural scientists, in collaboration with colleagues from Yonsei University and National Masan Tuberculosis Hospital in Busan, South Korea, are establishing a center of excellence for the study of MDR-TB. The center will address the basic biology underlying the development of drug resistance and serve as a clinical site for the evaluation of novel anti-TB agents.

DIR scientists also are studying the contribution of biofilms—communities of microorganisms embedded in a mucoidal (slime) matrix—to drug resistance. A bacterium often associated with biofilms, *Staphylococcus epidermidis*, is the most common pathogen in hospital-acquired infections and is responsible for healthcare costs of more than \$1 billion per year. Although usually a harmless bacterium of human skin, *S. epidermidis* can cause septicemia or endocarditis in patients undergoing immunosuppressive therapy, in premature newborns, or in injection drug users. However, most infections occur after the insertion of indwelling devices such as catheters or prosthetic heart valves. In these cases, the ability of *S. epidermidis* to form biofilms represents the most important virulence determinant. In a biofilm, the bacteria are dramatically less susceptible to antibiotic treatment and to attacks by human immune defenses. For these reasons, *S. epidermidis* infections are very difficult to eradicate. DIR scientists propose that drugs preventing and/or targeting biofilm formation will be of extraordinary use in antistaphylococcal therapy because they will enable the immune system to cope with an infection and increase

the efficiency of common antibiotics. To provide the scientific basis for the development of drugs interfering with biofilm formation, DIR scientists are investigating the molecular biology, biochemistry, and epidemiology of biofilm formation. This investigation includes studying specific factors contributing to biofilm formation, their regulation, and the interaction of biofilm-forming *S. epidermidis* strains with the host. The scientists recently defined the first factor of

the staphylococcal biofilm matrix that protects against major components of human innate host defense. This factor may provide a new target for antibacterial drugs.¹⁴

NIAID will continue collaborating with industry in order to stimulate and augment research into antimicrobial resistance and continue the development of novel products to address resistant bacterial infections in healthcare settings.

ASTHMA AND ALLERGIC DISEASES

Allergies are the result of inappropriate immune responses to normally harmless substances. Allergy symptoms vary widely, from the sneezes, watery eyes, and congested nose of mild “hay fever” to severe rashes, swelling, and shock. Asthma is a chronic inflammation of the lungs that airborne allergens can trigger in susceptible people; tobacco smoke, air pollution, viral respiratory infections, or strenuous exercise can also contribute. Asthma and allergic diseases can significantly decrease quality of life, employee productivity, and school attendance; in severe cases, they can be life threatening. The goal of NIAID’s asthma and allergic diseases research program is to develop more effective treatments and prevention strategies.

Allergies are the sixth leading cause of chronic disease in the United States and cost the healthcare system \$18 billion annually.¹⁵ About half of all Americans test positive for at least one of the 10 most common allergens¹⁶ (ragweed, Bermuda grass, rye grass, white oak, Russian thistle, *Alternaria* mold, cat, house dust mite, German cockroach, and peanut), and about 50 million suffer from allergic diseases each year. Food allergy occurs in 6 to 8 percent of children aged 6 years or younger and in 2 percent of adults.¹⁷ Common food allergens include cow’s milk, eggs, shellfish, and nuts; peanuts and tree nuts are the leading causes of fatal and near-fatal food allergy reactions.

The prevalence of asthma is also high. In 2002, 20 million people living in the United States currently had asthma; approximately 12 million people, including 4.2 million children younger than 18 years, had experienced an asthma attack in the previous 12 months.¹⁸ Asthma is much more prevalent among non-Hispanic Blacks than among non-Hispanic Whites and Hispanics, especially in children. For reasons that are still unclear, the prevalence of both allergy and asthma in the United States is increasing.



Magnified image of the common dust mite, which causes allergic responses in people.

The causes, pathogenesis, diagnosis, treatment, and prevention of asthma and allergic diseases are major areas of emphasis for NIAID’s Division of Allergy, Immunology, and Transplantation. NIAID vigorously pursues research on asthma and allergic diseases by supporting investigator-initiated projects, cooperative clinical studies, a national network of research centers, and demonstration and education research projects.

In 2004, NIAID invited applications to establish the Food Allergy Research Consortium, a collaborative research program designed to develop new approaches to treat and prevent food allergy. The program goals are to develop immune intervention strategies for preventing and treating food allergy; identify the mechanisms of development, loss and re-emergence of oral tolerance; determine the molecular and functional characteristics of food allergens; and determine the role of the gastrointestinal tract in development and loss of oral tolerance.

The Inner-City Asthma Study, co-funded by NIAID and the National Institute of Environmental and Health Sciences (NIEHS), was a multicenter, randomized controlled trial that tested the effectiveness of two interventions in reducing asthma morbidity among inner-city children with moderate to severe asthma; the study concluded in 2001. One intervention provided physicians with more detailed and up-to-date information on participants’ recent asthma symptoms and medication use. The other

intervention reduced exposure to environmental triggers such as tobacco smoke and allergens derived from cockroaches, house dust mite, mold, furry pets, and rodents. Participants were evaluated during both the 1-year intervention and for a 1-year follow-up period. The environmental intervention substantially lowered levels of cockroach and house dust mite allergens in the patients' environments, and this reduction was directly related to a decrease in asthma symptoms. The results of this study highlight the role of indoor allergens and tobacco smoke in determining asthma severity in inner cities and demonstrate that environmental interventions can substantially improve symptoms.

One project within the Inner-City Asthma Study evaluated the impact of indoor and outdoor fine particles and co-pollutants on respiratory illnesses. Recently published data from this study, which was funded by NIAID, NIEHS, and the U.S. Environmental Protection Agency, demonstrate that approximately 25 percent of the indoor particle concentration is contributed by outdoor particles. These data also show that smoking is the major source of indoor particles and that indoor concentrations of fine particles peak in the late evening in homes where smoking occurs, perhaps reflecting the influence of after-dinner smoking. Analysis of data pertaining to the effects of particle concentrations on asthma symptoms is currently underway.

The Inner-City Asthma Consortium (ICAC) is a NIAID-funded research network that evaluates the safety and efficacy of immune-based therapies to reduce asthma severity and prevent disease onset in inner-city children, investigates the mechanisms of action of the immune-based therapies, develops and validates biomarkers of disease progression, and investigates the immunopathogenesis of asthma in inner-city children. In FY 2004, ICAC initiated a cockroach allergen standardization protocol, a study to evaluate the usefulness of measurements of exhaled nitric oxide in the clinical management of asthma in children, and a birth cohort to

investigate the allergic and environmental factors that contribute to the development of asthma in inner-city children. The birth cohort project is being conducted at four sites and will enroll 500 newborns.

NIAID supports 13 Asthma and Allergic Diseases Research Centers (AADRCs), which are the cornerstone of the pathobiology component of the NIAID asthma and allergy research portfolio. The AADRCs conduct basic and clinical research on the mechanisms, diagnosis, treatment, and prevention of asthma and allergic diseases.

NIAID and the National Heart, Lung, and Blood Institute cosponsor the Immune System Development and the Genesis of Asthma program, which supports research on changes in immune function that occur early in life and lead to the development of asthma. Identification of the cellular and molecular processes involved in the onset of asthma will provide the basis for devising novel and effective new immune-based strategies for asthma treatment and prevention that do not compromise the integrity of the immune system.

The Immune Tolerance Network (ITN) is an international consortium of basic scientists and clinical investigators that performs clinical research to evaluate the safety and efficacy of methods that can induce the immune system to tolerate certain antigens, including allergens, for the treatment of immune-mediated disorders. ITN, which is co-sponsored by NIAID, the National Institute of Diabetes and Digestive and Kidney Diseases, and the Juvenile Diabetes Research Foundation International, has completed one trial of DNA-ragweed allergen conjugates for the treatment of allergic rhinitis. Preliminary data suggest that patients who received this conjugate prior to the 2001 ragweed season experienced fewer allergy symptoms during both the 2001 and 2002 ragweed seasons. ITN is currently conducting a phase II placebo-controlled trial to evaluate the safety and efficacy

of another treatment for ragweed allergy, which involves treatment with omalizumab, an anti-IgE antibody, and immunotherapy. A followup study will examine whether this treatment creates persistent immunologic and clinical tolerance. More information on ITN is available at www.immunetolerance.org.

In FY 2004, NIAID established the Atopic Dermatitis and Vaccinia Network to develop short- and long-term approaches to reduce the incidence and severity of eczema vaccinatum and protect individuals with atopic dermatitis from adverse consequences of vaccinia exposure.

An important NIAID intramural study is examining how allergen immunotherapy (AIT) reduces or prevents reactions to allergens such as

pollen, dust, or cat dander. Although the efficacy of AIT in asthma is modest, it is nonetheless the only disease-modifying therapy for allergic asthma currently known. Certain types of white blood cells, called Th2 cells, produce substances that contribute to the development of allergies, while others, called Th1 cells, produce substances that may inhibit the development of allergies. This study will determine whether AIT changes the immune response to allergens by reducing the number of Th2 cells or by converting them into Th1 cells. A better understanding of the mechanisms underlying the clinical effectiveness of AIT might help scientists to discover new approaches to treating allergies and asthma.

AUTOIMMUNE DISEASES

The immune system is essential to survival, and even a modest decrease in immune function can leave a person susceptible to infection. But the immune system itself can also *cause* disease, by inappropriately attacking the body's own organs, tissues, or cells.

More than 80 autoimmune diseases have been described to date. Some, such as type 1 diabetes, attack specific organs while others, such as systemic lupus erythematosus (SLE), involve multiple organs. Although many autoimmune diseases are rare, collectively they affect approximately 5 to 8 percent of the U.S. population. A disproportionate number of people with autoimmune disorders are women. For unknown reasons, the prevalence of autoimmune diseases is increasing.

NIAID's Division of Allergy, Immunology, and Transplantation (DAIT) supports a broad range of basic and clinical research programs in autoimmunity. Basic research focuses on understanding the genetics of autoimmunity, elucidating the mechanisms of self-tolerance, developing approaches to induce self-tolerance, and characterizing pathways of immune-mediated tissue destruction. Knowledge gained from basic research studies provides the rationale for clinical strategies to diagnose autoimmune diseases and to develop novel treatments for ongoing disease.

In response to Congressional interest in autoimmune diseases, NIH established the Autoimmune Diseases Coordinating Committee (ADCC) in 1998 to coordinate research on autoimmune disorders. Participation in this committee is very broad, and includes the directors, or their designees, of each of the NIH Institutes and Centers involved in autoimmune disease research; representatives of other Federal agencies, including the Centers for Disease Control and Prevention and the Food and Drug Administration, whose programs include

health functions or responsibilities relevant to these diseases; and representatives from a number of private organizations concerned with autoimmune diseases.

As required by the Children's Health Act of 2000, ADCC prepared the Autoimmune Diseases Research Plan and presented it to Congress in late 2002; the plan is available to the public at www.niaid.nih.gov/dait/pdf/ADCC_Report.pdf. In early 2005, the ADCC expects to submit its third progress report to Congress, which will summarize FY 2003 NIH funding, research accomplishments, and programmatic activities in autoimmune diseases research.

In addition to its basic autoimmune research portfolio, DAIT supports several clinical research programs on autoimmune diseases. The Autoimmunity Centers of Excellence facilitate close interactions between clinicians and basic researchers to promote collaborative research on autoimmune diseases, including single-site and multisite pilot clinical trials of immunomodulatory therapies; this program recently expanded from four to nine centers. Numerous clinical trials of treatments for SLE are underway or planned, including an ongoing trial of the clinical and immune effects of the immunosuppressant drug sirolimus and a test of a B cell-specific monoclonal antibody.

The Autoimmune Disease Prevention Centers conduct research on the development of new prevention strategies for autoimmune diseases and evaluate these approaches in pilot and clinical studies. In FY 2004, the Prevention Centers supported 16 pilot projects to test innovative prevention approaches or methods to measure biomarkers of autoimmune disease progression.

NIAID, in partnership with the National Institute of Diabetes and Digestive and Kidney Diseases, and the Juvenile Diabetes Research Foundation International (JDRF) co-sponsors the Immune Tolerance Network (ITN). This international consortium of more than 80

scientists and physicians is dedicated to the discovery and evaluation of methods that can induce stable, long-term immune tolerance in patients with many immune-mediated disorders, including autoimmune disorders. Tolerance strategies attempt to reprogram immune cells so that they no longer attack the patient's own tissues, but still effectively guard the body against infection. Because tolerance-inducing therapies would eliminate the need for lifelong immunosuppressive drug regimens—which themselves have serious side effects—they have the potential to revolutionize the management of many autoimmune diseases. The network has established several state-of-the-art core facilities and has supported 18 approved clinical protocols, as well as several additional studies of the immune mechanisms involved in tolerance. More information on ITN is available at www.immunetolerance.org.

Another group, the Stem Cell Transplantation for Autoimmune Diseases Consortium, is developing clinical trials to assess the efficacy of hematopoietic stem cell transplantation in the treatment of multiple sclerosis, SLE, and scleroderma. These complex trials are expected to open in 2005. The consortium will also conduct studies of the underlying immune mechanisms of these diseases as the trials progress.

DAIT supports three genetics research resources for autoimmune diseases. The Multiple Autoimmune Disease Genetics Consortium collects clinical data and genetic material from families in which at least two individuals have two or more autoimmune diseases. The data and samples will be made available to researchers studying the genetics of susceptibility or resistance to autoimmune diseases. More information can be found at www.madgc.org.

The North American Rheumatoid Arthritis Consortium (NARAC) collects clinical data and genetic material from families with rheumatoid arthritis. These data are made available to investigators to facilitate the characterization of

the genes underlying susceptibility to rheumatoid arthritis. NARAC is jointly supported by DAIT, National Institute of Arthritis and Musculoskeletal and Skin Diseases, and the Arthritis Foundation. More information can be found at www.naracdata.org.

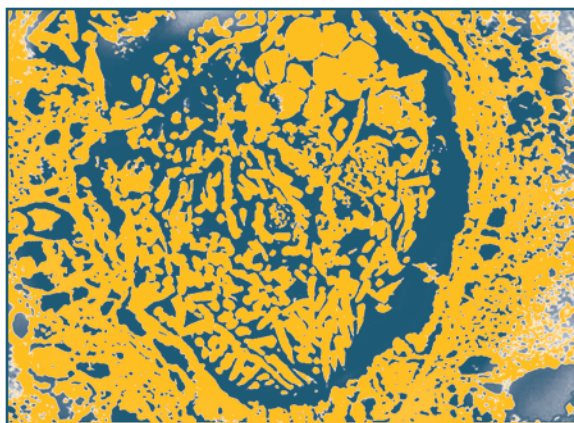
The International Histocompatibility Working Group (IHWG) is a network of more than 200 laboratories in over 70 countries that collect and share data on genes of the human leukocyte antigen (HLA) complex; this complex controls key steps in the immune response, especially those related to recognition of specific antigens. IHWG studies five diseases for which the HLA associations have been well characterized: type 1 diabetes, rheumatoid arthritis, celiac disease, narcolepsy, and spondyloarthropathy. The Working Group is supported jointly by NIAID, several other NIH Institutes, and JDRF. In addition, NIAID supports a project within the IHWG to identify single nucleotide polymorphisms (SNPs) in immune response genes. These variations may account for the increased susceptibility of certain individuals or groups to immune-mediated diseases. To date, SNP data have been gathered for over 100 genes related to the immune response. More information is available at <http://www.ihwg.org>.

Although researchers have made considerable progress in understanding the immune mechanisms that mediate tissue injury in autoimmune diseases, much remains to be learned. In particular, scientists are studying the causes of these diseases, the genetic factors that make people susceptible to them, and the regulatory mechanisms that control autoantibody production. NIAID is committed to advancing the understanding of how and why autoimmune diseases occur, and to promoting the application of basic research to clinical investigations in order to develop more effective therapeutic approaches and prevention strategies.

BIODEFENSE

A terrorist attack on the United States using biological agents, once thought to be a remote possibility, occurred in the fall of 2001 when *B. anthracis* spores were sent through the United States mail, causing 18 confirmed cases of anthrax (eleven inhalation, seven cutaneous). Recent events have raised awareness of both the possibility of a bioterrorist attack and the vulnerability of the U.S. population to such an event. In 2003 and 2004, ricin was found in an envelope at a postal facility in South Carolina and a Senate Office Building in Washington, DC, and it was used to contaminate several jars of baby food in California. Although the Department of Defense has developed defenses for biological warfare, there are additional concerns that need to be addressed to provide an adequate civilian defense from a bioterrorist attack. The number of microbial pathogens that threaten civilian populations is larger than that of classical biological warfare threats. Moreover, the populations to be protected are different because civilians include people of all ages and physical conditions.

In 2002, NIAID developed a strategic plan for biodefense research that outlines plans for addressing research needs for bioterrorism and emerging and re-emerging infectious diseases. In addition, NIAID convened a Blue Ribbon Panel of experts to provide objective scientific advice on NIAID's biodefense research agenda on so-called Category A agents. This list, which is defined by the Centers for Disease Control and Prevention, includes the most dangerous threat agents, such as smallpox and anthrax. The expert panel was asked to assess the current research, identify goals for the highest-priority areas, and make recommendations to achieve the goals. In the fall of 2002, NIAID convened a similar expert panel to assess current research and identify goals for Category B and C agents. In the areas of immunology and biodefense, NIAID has convened two more advisory bodies:



Bacillus anthracis, the rod-shaped organism that causes anthrax.

an Expert Panel on Immunity and Biodefense, to assess future immunology research most important to combat bioterrorism and emerging infectious diseases; and an Expert Panel on Atopic Dermatitis and Vaccinia Immunization, to develop a research plan to reduce the risk of eczema vaccinatum, a serious and sometimes deadly complication of smallpox immunization in atopic dermatitis patients.

In the past year, NIAID has continued to expand, intensify, and accelerate its ongoing research programs in biodefense. NIAID has launched research initiatives in areas ranging from the basic biology of microbes and their interactions with the human immune system to preclinical and clinical evaluation of new therapeutics and vaccines. These initiatives are designed to take advantage of the recent outpouring of ideas from academic and industrial scientists on ways to understand and combat potential agents of bioterrorism (www2.niaid.nih.gov/biodefense). In addition, NIAID released two progress reports highlighting accomplishments in biodefense research during the 18 months subsequent to the development of the strategic plan (www.niaid.nih.gov/biodefense/research/category_a_progress_report.pdf; www.niaid.nih.gov/biodefense/research/category_bc_progress_report.pdf).

Basic Research

One of the most important basic research tools that has evolved in recent years is the ability to rapidly sequence the entire genomes of microbial pathogens, including potential agents of bioterrorism. This capability allows scientists to identify microbial genes that play a role in disease and then design drugs that can block the activities of the proteins encoded by these genes. NIAID has made a significant investment in the DNA sequencing of the genomes of microorganisms considered agents of bioterrorism, including several Category A, B, and C agents. Organisms NIAID has helped to sequence include *Brucella suis*, *Burkholderia mallei*, *Clostridium perfringens*, *Coxiella burnetii*, *Rickettsia typhi*, *Staphylococcus aureus*, *Yersinia pestis*, *Mycobacterium tuberculosis*, *Vibrio cholerae*, *Cryptosporidium parvum*, *Giardia lamblia*, *Entamoeba histolytica*, *Toxoplasma gondii*, diarrheagenic *Escherichia coli*, *Shigella*, and *Salmonella*. In addition, NIAID has expanded its sequencing efforts of *B. anthracis* beyond the Ames strain used in the 2001 attack and has developed a comprehensive genomic analysis that includes sequencing of at least 14 additional strains, clinical isolates, near neighbors, and related species. These sequences will facilitate forensic strain identification; understanding of microbial pathogenesis; discovery of new targets for drugs, vaccines, and molecular signatures; and discovery of biomarkers for diagnostics to combat bioterrorism.

To expand its current enteric pathogens research network, NIAID established the Food and Waterborne Diseases Integrated Research Network to include multidisciplinary research on all food- and water-borne pathogens or toxins. The network also will facilitate the development and evaluation of products to rapidly identify, prevent, and treat food- and water-borne diseases that threaten public health.

Immunity and Biodefense

Considerable knowledge about the mechanisms of host immune responses to microbial pathogens

has been gained in recent years. Studies of innate immune mechanisms, which serve as a nonspecific first line of defense against pathogenic infection, have been especially productive. For example, the identification and functional characterization of the Toll-like family of receptors expressed on cells that mediate human innate immunity have led to an explosion of information now being applied to the development of new vaccine adjuvants and immunostimulatory agents to boost nonspecific immune protection. Additional progress on understanding the molecular mechanisms responsible for pathogen-specific immunity mediated by antibodies and cytotoxic T cells has led to new approaches in vaccine design. For example, NIAID-sponsored scientists identified two short peptides from vaccinia—the benign virus used as a smallpox vaccine—that are recognized by the immune systems of people who have been immunized. Researchers can use these peptides to track the human immune response to the virus as they try to develop an improved vaccine. Finally, the threat of bioterrorism and the natural emergence of diseases due to microbes such as West Nile virus and severe acute respiratory syndrome (SARS) virus underscore the importance of defining the immune parameters responsible for increased susceptibility to infectious diseases of infants, young children, the elderly, and immunocompromised individuals.

To gain a better understanding of the human immune response to potential agents of bioterror, NIAID funded eight Cooperative Centers for Translational Research on Human Immunology and Biodefense. These centers, located throughout the country, focus on rapid development of bioterrorism countermeasures, such as vaccines and therapies.

Also contributing to the biodefense vaccine effort are a number of recent contracts awarded to identify immune epitopes for Category A, B, and C pathogens; define human genetic variance that contributes to infection susceptibility or vaccine efficacy; identify new candidates for

vaccine adjuvants; develop reagents for nonhuman primate studies of new drug or vaccine candidates; and address the problem of eczema vaccinatum as a serious adverse consequence of the current smallpox vaccine.

New Diagnostic Tools

NIAID also supports research leading to the development of new and improved diagnostics. The goals of this research are to establish methods for the rapid, sensitive, and specific identification of natural and bioengineered microbes, as well as to determine the microbes' sensitivity to drug therapy. Progress in these areas will allow healthcare workers to diagnose and treat patients more accurately and quickly.

In FY 2004, NIAID developed two initiatives that specifically support the development of the next generation of medical diagnostics—Challenge Grants: Biodefense and SARS Product Development; and Cooperative Research for the Development of Vaccines, Adjuvants, Therapeutics, Immunotherapeutics, and Diagnostics for Biodefense and SARS. Under these initiatives, 45 awards were made in FY 2004. NIAID also continues to support its Small Business Biodefense Program, which encourages the development of therapeutics, vaccines, adjuvants/immunostimulants, diagnostics, and selected resources for biodefense by the small business research community. This program expands the duration and dollar limits for small business grants to develop specified products that are considered high priority for biodefense.

NIAID supports a range of biodefense genomics research projects that provide comprehensive genomic, bioinformatics, functional genomics, and proteomic research resources to the scientific community to help researchers identify targets and proteins for use in new diagnostics. Through these projects, NIAID awarded contracts in FY 2004 for eight Bioinformatics Resource Centers to develop and maintain comprehensive, relational databases for genomic and related

data for microorganisms responsible for emerging and re-emerging infectious diseases and for those considered agents of bioterrorism (www.niaid.nih.gov/dmid/genomes/brc/default.htm). NIAID also awarded contracts for seven Biodefense Proteomics Research Centers and one coordinating center to develop and enhance innovative proteomic technologies and methodologies and apply them to the understanding of the pathogen and/or host cell proteome for the discovery and identification of novel targets for the next generation of drugs, vaccines, diagnostics, and immunotherapeutics against microorganisms considered agents of bioterrorism (www.niaid.nih.gov/dmid/genomes/prc/default.htm). In addition, the NIAID-supported Pathogen Functional Genomics Resource Center was expanded to provide the infectious disease research community with state-of-the-art research and reference reagents that can be used in the development of diagnostics or other products.

Vaccines

NIH-supported researchers are developing vaccines against many infectious agents, including those considered to be bioterrorism threats, for use in civilian populations of varying ages and health status. Vaccines are being developed using both traditional and novel technologies. Significant progress has been made in the development of next-generation vaccines for anthrax and smallpox, and in the development of new vaccines for Ebola and West Nile viruses.

In 2003, NIAID awarded four contracts to fund development of new vaccines against smallpox, plague, and tularemia. The smallpox contract awards continue advanced development work that began in February 2003 on two modified vaccinia Ankara (MVA) vaccine candidates. These new contracts will support larger-scale manufacturing of the vaccines, as well as further safety and efficacy studies in animals and humans. The tularemia and plague contract awards will fund early-stage product development of the respective

vaccines, including dosage formulation, pilot batch production, and initial clinical assessment.

Therapeutics

NIH therapeutics research focuses on the development of new antimicrobials and antitoxins, as well as the screening of existing antimicrobial agents to determine whether they have activity against organisms that might be used by bioterrorists. Knowledge gained from basic and applied research is helping to identify additional targets for medications and immune-based therapies against agents of bioterrorism.

In FY 2004, NIAID made additional awards to expand the resource pool in the *In Vitro* and Animal Models for Emerging Infectious Diseases and Biodefense Program to provide a range of resources for preclinical testing of new therapies and vaccines, including nonhuman primate models.

NIAID also has expanded the Collaborative Antiviral Study Group (CASG) by approximately 20 percent since it was established in 1986. In 2003, CASG developed a clinical protocol for the treatment of smallpox with cidofovir, in the event of an outbreak or release. NIAID is currently supporting a phase I clinical study by Chimerix, Inc. to assess initial safety, tolerability, and pharmacokinetics of a promising new oral derivative of cidofovir in normal volunteers. The CASG will conduct future phase I/II studies with the drug after the initial phase I study is complete.

Research Resources

Over the past year, NIAID has continued to devote considerable resources to the expansion of centralized laboratory resources, including regional biosafety laboratories, *in vivo* and animal model resources, drug screening contracts, the production of standardized and validated reagents and tests, and genomic and bioinformatics resources. The availability of such resources assists

the research community in conducting studies of biodefense pathogens.

Biodefense and Emerging Infections Research Resources Repository

NIAID established the Biodefense and Emerging Infections Research Resources Repository in September 2003 to provide unique and quality-assured biodefense-related reagents and resources to the scientific community. This program helps facilitate the understanding of the pathogenesis of NIAID category A, B, and C priority pathogens and emerging infectious diseases organisms, and may aid in the development and evaluation of vaccines, therapeutics, and diagnostics for these organisms. The repository also coordinates access to reagents not held in the program.

In order to facilitate research and product development for biodefense and emerging infectious diseases, the repository is collecting information about biodefense-related reagents and standards and will disseminate this information through print, electronic media, and workshops; enhance technology transfer through development and publication of methods; and facilitate commercial development of reagents through proactive communication with biotechnology and pharmaceutical companies. In addition to securing acquisition, storage, and the distribution of biological agents, the repository will also generate new reagents as scientific advances are made.

It is anticipated that in the long-term the Biodefense and Emerging Infections Research Resources Repository will become the Federal government's national resource and clearinghouse for specimens, reagents, and information on these organisms. By centralizing this function, access to and use of these materials can be monitored and quality control of the reagents assured. Information about this resource is now available on the Web site at www.beiresources.org.

NIAID Intramural Research Programs

Biology of the Microbe

The NIAID Division of Intramural Research (DIR) studies of *B. anthracis*, the bacterium that causes anthrax, are focused on identification, genetic regulation, and analysis of the anthrax toxin and other virulence factors, as well as development of improved vaccines and therapeutics. The anthrax toxin is the primary cause of damage to animal tissues during an anthrax infection. Recent NIAID intramural studies of anthrax toxin aim to identify organs, tissues, cells, and proteins targeted by anthrax lethal toxin; characterize the contribution of anthrax edema toxin and capsule to pathogenesis; and define the molecular details of the interaction of anthrax toxin with its receptors. In addition, scientists plan to identify changes in the proteome of tissues damaged by anthrax toxin and measure the ability of anti-capsule antibodies to protect against anthrax infection.

NIAID intramural investigations of *Yersinia pestis*, the bacterium that causes plague, have resulted in the development of both mouse and rat models of bubonic plague that incorporate the natural flea-borne route of transmission. A new plague vaccine candidate developed by the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) was recently found to be 100 percent effective in the NIAID mouse model.¹⁹ This work is important to NIAID's biodefense efforts as well as to efforts to control naturally occurring plague epidemics. In light of recent plague outbreaks in human populations in India and Africa and the emergence of multiple antibiotic-resistant strains of *Y. pestis*, plague remains an international public health concern.

To better understand the innate immune response, DIR scientists are studying infection-fighting white blood cells called neutrophils, which are an essential part of human innate immunity. Although much is understood about the innate immune response to infection, the

molecular basis for termination of inflammation and resolution of infection in humans is not clearly understood. To that end, NIAID researchers have produced a comprehensive new picture of the interactions between many kinds of disease-causing bacteria and neutrophils. By describing changes in neutrophil gene expression in response to bacterial invasion, the investigators have identified dozens of possible targets for drug therapies. These findings are likely to be broadly applicable to many types of microorganisms that cause disease in humans, and could lead to new treatments that augment the immune response against multiple high-priority pathogens.²⁰

Additional investigations underway in NIAID laboratories include studies of the pathogenesis of *C. burnetii*, the agent of Q fever; studies of multidrug-resistant tuberculosis; studies of relapsing fever agents with a focus on improving diagnostic tests; and a new program to identify and characterize antigens suitable for use in a vaccine against *Burkholderia mallei* and *Burkholderia pseudomallei*, the causative agents of glanders and melioidosis, respectively. This research is supported by enhanced genomics and proteomics capabilities on the Bethesda campus and at the Rocky Mountain labs.

Vaccines

NIAID has a longstanding intramural research program aimed at shedding light on the molecular biology and gene expression mechanisms used by vaccinia—the virus used in the current smallpox vaccine—and other poxviruses. A primary aim of this program is the development of MVA as a carrier for the delivery of vaccine components and gene therapies to target cells. Intramural poxvirus researchers, who have decades of experience with MVA, and other poxvirus scientists are collaborating with USAMRIID researchers and others in nonhuman primate studies of MVA's efficacy as a smallpox vaccine. In a study comparing MVA and Dryvax in a monkey model, scientists found that after two doses of MVA or one MVA dose followed by

Dryvax, the immune response was equivalent or higher than that induced by Dryvax alone. After challenge with monkeypox virus, unimmunized animals developed hundreds of skin lesions and became gravely ill or died, whereas vaccinated animals were healthy and asymptomatic, except for a small number of transient skin lesions in animals immunized only with MVA. These findings are important steps in the evaluation of MVA as a replacement vaccine or pre-vaccine for those with increased risk of severe side effects from Dryvax.²¹

In addition, researchers at the Vaccine Research Center (VRC) are working to complete two phase I clinical trials in which MVA is evaluated in both vaccinia-naïve (never vaccinated) and vaccinia-immune (previously vaccinated against smallpox) populations.

Hemorrhagic fevers such as those caused by Ebola virus are associated with a high mortality rate, particularly for the Ebola Zaire subtype. Traditional public health measures to prevent future outbreaks are limited, thus increasing the urgency for development of an effective vaccine. An interagency agreement currently in place between NIAID and USAMRIID allows for collaboration in animal studies, assay performance, and data analysis.

A potentially effective adenoviral vector-based (ADV) vaccine for Ebola virus infection in nonhuman primates has been developed under an interagency agreement between NIAID and USAMRIID. An ADV-only vaccine that elicited protective immunity in monkeys after a 4-week postvaccination challenge, in contrast to previous 10-week or 6-month vaccine regimens, could be especially useful in an acute Ebola outbreak, if the vaccine proves as effective in humans. A second-generation product may also be evaluated that could potentially provide coverage for Marburg and possibly Lassa viruses. In addition, the VRC began a phase I trial of a DNA-based vaccine for Ebola in November 2003.

The VRC is currently conducting preclinical testing of a West Nile virus vaccine. The VRC proposes to use an existing codon-modified gene-based DNA plasmid vaccine platform to make DNA constructs that express West Nile virus proteins. These vaccine constructs are currently undergoing immunogenicity and viral challenge studies in rabbits. The VRC, in collaboration with Vical, Inc., has completed good manufacturing practices production of the vaccine for a phase I trial scheduled for early 2005.

Therapeutics

NIAID clinical investigators have an approved protocol in place that will allow them to evaluate and treat persons exposed to or infected with anthrax and to conduct immunologic evaluations of recipients of anthrax vaccines. In addition, DIR investigators and their colleagues in the NIH Clinical Center are collecting serial blood samples and throat swabs from healthy persons who receive the smallpox vaccine in order to measure serum cytokines and look for the smallpox vaccine virus. Identification of specific cytokines induced after vaccination may help to explain certain side effects associated with the smallpox vaccine and suggest new ways to modify some of these side effects. Investigators also are evaluating different methods of detecting the smallpox vaccine virus in clinical specimens, including sensitive cell culture methods and polymerase chain reaction.

Protective antibodies are produced by the host in response to infection or immunization. Administration of sera containing protective antibodies to people exposed to a pathogen is called passive immunoprophylaxis and has long been used to prevent disease in exposed populations. However, monoclonal immunoglobulin preparations tailored to act specifically on the most vulnerable parts of an invading pathogen could be of higher and more consistent potency.

DIR researchers are pursuing several prophylaxis and treatment strategies based on monoclonal antibodies, including the development of preparations that can be used to prevent or treat complications of smallpox vaccination, smallpox, anthrax, SARS, West Nile virus, botulism, rabies virus, Japanese encephalitis virus, and the tick-borne encephalitis virus complex. For example,

DIR researchers are developing preparations of monoclonal antibodies from chimpanzees—which are virtually identical to human antibodies—that can bind specific antigens on the vaccinia virus and might therefore be used in treatment of complications arising from the use of this virus as a smallpox vaccine.

BIOENGINEERING, BIOINFORMATICS, AND ADVANCED TECHNOLOGIES

Bioengineering, bioinformatics, and other advanced technologies provide crosscutting tools that facilitate research in many disciplines. Bioengineering combines physics, chemistry, and mathematics, as well as basic engineering principles to enhance the study of biology, medicine, behavior, and health. Bioinformatics and computational biology apply computer science and advanced mathematics to the fields of biology and medicine to enable integration and analyses of biological, medical, behavioral, and health data. Other advanced technologies, such as biomedical imaging, proteomics, and genomics, facilitate characterization of complex biological processes.

The powerful tools and techniques of bioengineering, bioinformatics, and computational biology extend the capacity of science to perceive, capture, and manage information about biological processes. They have become integral components of NIAID-supported basic and clinical immunology research. Additional technologies, including proteomics, biosensor fabrication, biomedical imaging, and data integration, also are becoming important tools for researchers. Below are examples of NIAID-supported programs in these areas.

- **Mass spectrometry for high-throughput peptide characterization.** This program supports the development of chemical measurement instruments for the sequence analysis of peptide antigens presented in the major histocompatibility complex (MHC). The goal of this research is to develop a high-throughput method to study peptides that are recognized by the body as “self.” Understanding how the immune system distinguishes between “self”—the body’s own organs, tissues, and cells—and “not self”—foreign and potentially harmful agents—is relevant to all immune-mediated diseases.
- **Biodefense Proteomics Collaboratory.** This program supports research to dissect immune responses to viruses that are potential agents of bioterrorism, utilizing proteomics approaches to characterize dynamic changes in protein expression in inflammatory cells after pathogen exposure. This information will be compiled in a publicly available database. Bioinformatics approaches also will be used to correlate observed changes in protein expression with available data on changes in gene expression due to inflammation induced by viral infection or endotoxin shock.
- **Proteomics Research Centers: identifying targets for therapeutic interventions using proteomic technology.** The program will solicit proposals to identify proteins associated with the biology of microbes, host innate and adaptive immune response, and mechanisms of microbial pathogenesis. These projects will utilize and augment existing technologies or create novel proteomics approaches to perform early stage validation studies for identified proteins and cellular targets. To assist the centers, an Administrative Resource for Biodefense Proteomics Research Centers has been established. This resource will maintain a publicly available Web site that contains data and technology products generated by the Proteomics Research Centers. It will also monitor and facilitate the deposition of reagents and protein targets in a central repository. The Administrative Resource will coordinate programmatic meetings and the establishment of a scientific advisory board.
- **Systems approaches to innate immunity, inflammation, and sepsis.** This program supports research to create a comprehensive picture of innate immunity, the body’s first line of defense against bacterial, viral, and fungal diseases. This multidisciplinary

systems biology approach will lead to an understanding of molecular-level innate immune responses triggered by bacterial and viral infections. One member of this team recently discovered a single protein that acts as a key switch point in innate immune responses to both bacterial and viral infections. In determining how this protein functions, the team of scientists learned why certain symptoms, such as fever, occur regardless of the cause of infection.²²

- **Modular gene assembly.** Researchers are developing a new system for engineering genes on the basis of their binding and activation properties. This technology will enable the formation, selection, and assembly of genes based on individual functional traits, which could lead to the development of novel therapeutic compounds such as custom antibodies and immunosuppressants.
- **Microchip drug delivery system.** This program supports development of a novel drug delivery device that uses silicon-based microchips to deliver complex regimens of bioactive agents to specific organs or tissues. Researchers have demonstrated that a silicon-based microchip device with no moving parts can be operated *in vivo*. This device will allow for controlled delivery of a concentrated amount of drugs or bioactive compounds to affected tissue and has the advantage of eliminating possible toxic side effects and inefficient delivery of systemically administered compounds.
- **Alliance for Cellular Signaling (AfCS).** AfCS is a large-scale collaborative program co-funded by the National Institute of General Medical Sciences (NIGMS), NIAID, the National Cancer Institute, several pharmaceutical companies, and private sources. The primary goal of the AfCS is to dissect signaling pathways in mammalian cells in order to understand how cells interpret and respond to external signals. All of the materials and information developed through the AfCS are freely available to the biomedical community worldwide. More information is available at www.signaling-gateway.org.
- **NIGMS Protein Structure Initiative.** NIAID contributes to the support of this NIGMS-sponsored program to determine the structure of proteins from the genomes of pathogenic protozoans and malaria parasites. The program involves computer prediction of protein domains for target selection, high-throughput protein expression, crystallization, and structural analysis. More information is available at <http://www.nigms.nih.gov/psi/>.
- **Whole-organism imaging of immune response.** This program uses imaging technologies to detect the accumulation of labeled T cells and macrophages in organ transplants and to examine the development of systemic autoimmunity *in vivo*. The ability to monitor T cell migration to and accumulation in organs such as the liver, kidney, and bowel, or in the central nervous system is important to understanding immune responses to pathogens and immune-mediated diseases. Another NIAID-funded project is developing new magnetic resonance imaging contrast reagents (dyes) to track immune responses *in vivo*.
- **Genomic databases and analysis tools.** NIAID supports databases of genomic information and analysis tools for the multidisciplinary study of sexually transmitted pathogens, including pneumonias, chlamydia, papillomavirus, herpes, and gonorrhea. These tools, which include dynamic graphics and Web-based data mining and sequence analysis tools, extend beyond molecular sequence data. This resource is available from the Los Alamos National Laboratory and is also supported by the U.S. Department of Defense. See www.stdgen.lanl.gov for more information.

- **Bioinformatics Integration Support Contract (BISC).** The goal of BISC is to advance the discovery and testing of new therapies for immune-mediated diseases and to further understanding of the basis of innate and adaptive immunity by providing advanced computer support for scientific data handling and disseminating best practices in scientific data analysis. BISC will provide the means for scientists to easily access, generate, analyze, and exchange complex high-quality datasets. Specifically, BISC will provide a data repository, a suite of bioinformatics analysis tools, a suite of data integration tools, consulting advice on technical and data management issues, and an archive facility to scientific researchers funded by the NIAID Division of Allergy, Immunology, and Transplantation and the National Institute of Diabetes and Digestive and Kidney Diseases.
- **HIV Database and Analysis Unit.** This unit includes the HIV Genetic Sequence Database and the HIV Molecular Immunology Database. The Genetic Sequence Database compiles sequence information from GenBank and other international databases and then conducts indepth analyses of HIV genomes. The Molecular Immunology Database compiles all published immunologic information on humoral and cellular immune epitopes from HIV proteins. These databases also provide analysis tools to the user community at <http://hiv-web.lanl.gov> and <http://hiv-web.lanl.gov/immunology/index.html>.
- **Immune epitope database and analysis program.** The primary goals of this program are to develop and maintain an integrated, Web-based, searchable database of antibody binding sites (antibody epitopes) and antigenic MHC-binding peptides (T cell epitopes) for a wide variety of infectious agents and immune-mediated diseases, with emphasis on category A, B, and C bioterrorism agents as well as emerging and re-emerging infectious diseases. It is anticipated that the information contained within the database and the availability of analysis tools will facilitate identification of novel vaccine candidates and immunotherapeutic strategies to improve biodefense strategies. HIV epitopes are excluded; those data are already catalogued in the HIV Molecular Immunology Database at Los Alamos Laboratory.
- **Innovations in Biomedical Computational Science and Technology.** This trans-NIH program announcement was developed in response to a report by the NIH Working Group on Biomedical Computing. The report noted the continued need to improve the interface between biomedical research and biomedical information science and technology. This program promotes research and development in database design, graphical interfaces, query approaches, data retrieval, visualization, integration, and manipulation.

DRUG RESEARCH AND DEVELOPMENT

The discovery of sulfanilamide, penicillin, and other antibiotic drugs in the early 20th century revolutionized the treatment of infectious diseases and gave doctors powerful new tools that for the first time allowed them to easily defeat bacterial infections that would otherwise have been life-threatening. More recently, drugs have been developed that can combat viruses such as influenza and HIV, as well as fungal and parasitic infections. Unfortunately, many infectious agents have become resistant to current therapies, thereby threatening to destroy the effectiveness of these original “wonder drugs.” Also, the immune system can itself cause illnesses such as diabetes, arthritis, and multiple sclerosis when it inappropriately attacks the body’s own tissues.

The development of new therapies for the treatment of infectious and immune-mediated diseases is therefore one of NIAID’s highest priorities. Basic research is the foundation for drug development. Through scientific advances in microbiology, virology, and immunology, scientists identify potential targets for therapeutic agents and new strategies for treating infectious and immune-mediated diseases. Often in collaboration with industry, academia, and other Government agencies, NIAID carries out many research programs that facilitate drug development, including databases of chemical structures that can be screened for use as therapeutic agents, facilities to conduct preclinical testing of promising drugs, and clinical trial networks to evaluate the safety and efficacy of drugs and therapeutic strategies. Because drug development is a key component of NIAID’s mission, each NIAID division is actively involved in the drug development process.

Division of Acquired Immunodeficiency Syndrome

The Division of Acquired Immunodeficiency Syndrome (DAIDS) devotes a substantial portion

of its resources to the discovery and development of new therapies for people with HIV/AIDS, including AIDS-associated opportunistic infections, co-infections, and malignancies. DAIDS makes a special effort to provide funds to promising research strategies that receive insufficient support elsewhere.

A strong portfolio of basic research is the foundation for DAIDS’ drug development activities. Over the past 15 years, drug discovery efforts have concentrated on a relatively small number of HIV targets, especially reverse transcriptase (RT), the enzyme that makes a DNA copy of the virus’ RNA genome after it invades a cell, and protease (PR), the enzyme that activates immature HIV precursor proteins.

A combination of RT and PR inhibitors known as highly active antiretroviral therapy, or HAART, has revolutionized the treatment of people with HIV, successfully suppressing the virus and decreasing the incidence of opportunistic infections. These drugs, however, do not constitute a magic bullet. Many patients suffer metabolic abnormalities and toxicities, and some have difficulty adhering to the complex drug regimens required. Strains of HIV resistant to the therapy can also emerge.

Fortunately, new classes of therapeutic agents have recently entered the development pipeline. Some of these interfere with virus binding and entry into the cell, while others act on viral targets such as HIV integrase, an enzyme that incorporates the HIV genome into a host cell’s DNA. Stopping HIV before it integrates into a host cell is an attractive strategy because it would potentially protect healthy cells from infection and thereby prevent immune system dysfunction. Therapeutic vaccines, which attempt to spur the immune system of an infected person to mount a more vigorous defense, are a potential immunologic approach to complement drug treatment. Even as these advances continue, so, too, does the need for new host and viral targets, novel drugs and delivery systems, and

immunologic approaches to address the dual problems of drug resistance and toxicity.

The pathways that lead to new HIV drug therapies are many and varied, but all begin with basic research. The studies include the structure and function of viral and cellular proteins critical to the HIV life cycle, immunopathogenic studies to understand how the virus disables the immune system, genetic studies—both human and viral—to define which genes affect susceptibility to infection and disease progression, and studies to understand how to restore effective immune function.

DAIDS pursues these approaches to targeted drug discovery through investigator-initiated grants, Small Business Innovation Research grants, and contracts. Current programs targeting therapeutics research on HIV/AIDS, its complications, and co-infections include the Novel HIV Therapies: Integrated Preclinical/Clinical Program (IPCP); the Innovation Grants for AIDS Research program; the Therapeutics Research on AIDS-Associated Opportunistic Infections and Malignancies Program; the Liver and Pancreatic Disease in HIV Infection Program; the Complications of Antiretroviral Therapy Program; and the International Studies of AIDS-Associated Co-Infections Program (ISAAC).

The IPCP supports the preclinical evaluation, development, and pilot-stage clinical study of novel agents and strategies to suppress HIV replication, interfere with disease progression, reconstitute or repair immune damage, genetically protect cells against HIV, and ameliorate the consequences of infection. Once a novel therapeutic is identified and moves into preclinical development, it is systematically varied in small ways in an effort to improve its overall activity, safety, and effectiveness. These variations on a theme are subjected to additional *in vitro* testing, evaluating the agent's activity against a range of HIV isolates in different cell lines and animal models. If appropriate, the IPCP supports early clinical evaluation in human studies.

The Innovation Grants for AIDS Research Program supports research ideas that are new, innovative, or in the early stages of development, with the expectation that innovative research in these fields will increase understanding of the HIV pathogenesis and disease progression and provide new concepts for prevention and therapy. Targeted research for this program includes therapeutic discoveries, microbicide discovery, and HIV pathogenesis.

The Complications of Antiretroviral Therapy Program supports research in the fundamental biochemical or pathogenic mechanisms of the metabolic complications associated with HIV disease and antiretroviral therapy. Metabolic complications highlighted by this program include lipodystrophy (redistribution of body fat), insulin resistance, osteopenia (bone loss), abnormal lipid metabolism, and elevated lactate levels. This program is cosponsored by NIAID, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Institute on Drug Abuse, and the National Institute of Mental Health.

The ISAAC Program supports clinical studies of co-infections of HIV with one or more other pathogens such as tuberculosis (TB), other AIDS-defining opportunistic infections, malaria, and other parasitic infections endemic among adults and children in resource-constrained tropical countries. The long-term goals of ISAAC are to develop effective and sustainable clinical management strategies to improve local standards of care and to foster the integration of research for HIV and relevant co-pathogens. The program emphasizes training, technology development, and enhancing independent research capacities in host country sites.

The Therapeutics Research on AIDS-Associated Opportunistic Infections and Malignancies Program stimulates preclinical research for novel therapeutic strategies against opportunistic infections, co-infections, and malignancies in people with HIV/AIDS.

This program is sponsored jointly with the National Cancer Institute and the National Institute of Dental and Craniofacial Research. The AIDS-associated infections this program emphasizes are *Mycobacterium tuberculosis* (*M. tb*), *Pneumocystis carinii*, *Cryptosporidium parvum*, and the microsporidia. The AIDS-associated malignancies program focuses on Kaposi's sarcoma, lymphomas, cervical cancer, oral warts and cancers, and anogenital cancers.

The Liver and Pancreatic Disease in HIV Infection Program is intended to stimulate research on the pathogenesis and therapeutics of liver and pancreatic disorders associated with co-infections that occur in HIV patients, as well as the metabolic complications associated with treatment of HIV infection. This program is sponsored jointly with NIDDK. The co-infections that this program emphasizes include hepatitis B and hepatitis C. Metabolic complications include hepatic drug toxicity, hepatic lipid metabolism, nonalcoholic steatohepatitis, and pancreatitis.

Contract resources are also devoted to supporting clinical research on therapeutic interventions for *M.tb* infection and co-infection with HIV (see, for example, <http://www.taacf.org>). This support includes high-throughput screening of anti-*M.tb* compounds and testing in animal models. For additional information on *M.tb* research, see the section on TB on page 121.

DAIDS also supports therapeutics discovery and development by helping to acquire and disseminate information on promising treatments for treating HIV infection and associated opportunistic pathogens. These activities include assisting drug sponsors in obtaining additional *in vitro* and *in vivo* activity data. DAIDS also keeps track of treatments in the pipeline by developing, maintaining, and using databases of chemicals with known or potential activity against HIV and associated opportunistic pathogens. DAIDS scientific staff members use these databases to monitor compounds already under investigation and to identify additional candidates. Information

from the databases is available to the scientific community on request.

Once a therapy has been developed, DAIDS sponsors clinical trials to determine how well it improves the quality and duration of life for HIV-infected individuals; these clinical tests include studies to evaluate safety, dose, activity, efficacy, and optimal use. The trials are conducted through one of three large multicenter clinical trials networks—the Adult AIDS Clinical Trials Group, the Pediatric AIDS Clinical Trials Group, and the Terry Beirn Community Programs for Clinical Research on AIDS. Together, these groups comprise the largest AIDS clinical trials network in the United States, if not the entire world.

Division of Microbiology and Infectious Diseases

The Division of Microbiology and Infectious Diseases (DMID) supports the discovery and evaluation of new drugs for infectious diseases at all three phases of the process: discovery, preclinical evaluation, and clinical evaluation. Because DMID's mandate encompasses a broad array of infectious diseases, the Division's drug development efforts address the entire spectrum of infectious diseases, including hepatitis, herpes, TB, sexually transmitted infections (STIs), malaria, fungal diseases, viral respiratory infections, hospital-associated bacterial infections, and pneumonia. Moreover, the Division's activities support all stages of drug discovery and development, from the test tube to the bedside and, especially for animal model and clinical research, involve close collaborations with the pharmaceutical industry and the Food and Drug Administration (FDA). Finally, in FY 2004, DMID supported approximately 40 large-scale genome-sequencing projects; the genomic information obtained has great potential for further advancing the discovery and evaluation of new therapeutic agents for infectious diseases.

Discovery and Preclinical Evaluation

DMID maintains an active antiviral screening program that tests potential antiviral agents *in vitro* for activity against many different viruses, including herpes simplex viruses (HSV-1, HSV-2, varicella-zoster virus [VZV], Epstein-Barr virus, cytomegalovirus [CMV], human herpesvirus [HHV]-6, HHV-8); respiratory viruses (influenza A and B, respiratory syncytial virus, parainfluenza virus, measles, rhinovirus, adenovirus, sudden acute respiratory syndrome coronavirus); hepatitis B and C; papillomaviruses, BK virus, orthopoxviruses (vaccinia and cowpox); and other viruses that cause hemorrhagic fevers and encephalitides, including West Nile virus. DMID also collaborates with the U.S. Army Medical Research Institute on Infectious Diseases antiviral program in the search for therapies for exotic viruses such as Ebola and Sin Nombre. DMID and DAIDS staff members also interact closely on drug discovery research and therapeutic evaluation efforts for HIV therapies.

DMID supports basic and applied research on the discovery and design of antiviral agents; these projects have led to the design of new drugs for influenza, CMV, poxvirus, and hepatitis. Preclinical evaluations of antiviral therapies also are conducted in animal models of human viral infections. One part of a recent study, for example, included the development of a new mouse model for VZV infection in neurons. VZV causes both chickenpox and shingles; the new mouse model will increase our understanding of shingles and help in the development of new VZV vaccines and antivirals. Other recent findings have identified several drugs with activity against members of the poxvirus family, which might be helpful in the event of a bioterrorist attack using smallpox.

Basic research on pathogen replication has led to the identification of new therapeutic targets for viruses, bacteria, and parasites, which in turn opens up new possibilities for the development of drugs that attack these targets. For example,

DMID-funded malaria researchers are working to identify the unique biochemical pathways in the malaria parasite that could serve as drug targets. They are also determining the mode of action of existing and potential drugs and mapping out the mechanisms by which the parasite has become resistant to existing drugs.

The emergence of antibiotic-resistant pathogens, including those that cause pneumonia and TB, has become a serious global health threat. Methicillin-resistant *Staphylococcus aureus*, for example, has rapidly emerged as a community-associated infection, and in two separate instances, *S. aureus* has acquired genes that make it resistant to the powerful antibiotic vancomycin. Public health officials fear that a strain of *S. aureus*—or some other pathogen—might arise that resists all antibiotics currently available.

In response, the Public Health Service, under the leadership of the NIH, FDA, and the Centers for Disease Control and Prevention, developed an antimicrobial resistance action plan that provides a blueprint for specific coordinated government actions to address the emerging threat. The four areas of emphasis are (1) surveillance, (2) prevention and control, (3) research, and (4) product development. NIAID has the lead in the area of research. The original plan, *A Public Health Action Plan to Combat Antimicrobial Resistance, Part 1: Domestic Issues*, as well as the second annual progress report and activity inventory are available online at www.cdc.gov/drugresistance/actionplan.

Prompt and accurate diagnosis of an infection is obviously important for good patient care, because it allows doctors to choose the right antibiotic. But good diagnostic tools also help to preserve the efficacy of drugs we currently have, by helping to limit the exposure of pathogens to inappropriate treatments, and can aid in the identification of patient populations for the evaluation of new antimicrobial agents. At the end of FY 2004, DMID began a new research initiative, called “Sepsis and CAP: Partnerships

for Diagnostics Development,” that will support industry development of broad diagnostic technologies for early detection of major causes of septicemia, bacteremia, candidemia, and community-acquired pneumonia.

Clinical Studies

DMID supports clinical research with both individual grants and contract-supported programs such as the Collaborative Antiviral Study Group (CASG). The CASG, which evaluates antiviral drug therapies for neonatal and adult treatment of herpesvirus infections, is supported by a single award to the University of Alabama at Birmingham, and by subcontracts to more than 100 collaborating sites. The CASG also supports clinical trials that both assess the safety and efficacy of an experimental immunoglobulin treatment for West Nile virus encephalitis and help to elucidate its natural history.

The NIAID Mycoses Study Group (MSG), funded by both DMID and DAIDS, has supported clinical trials of antifungal therapies for opportunistic and endemic mycoses (fungal infections) since the 1970s. In early 2001, in conjunction with the scheduled completion of the MSG contract, two new contracts were awarded: the Bacteriology and Mycology Study Group (BAMSG) and the Bacteriology and Mycology Biostatistical and Operations Unit (BAMBU). BAMSG continues to conduct clinical trials of interventions for serious fungal diseases as well as healthcare-associated resistant bacterial infections. BAMBU provides biostatistical and administrative support for these clinical trials.

Other DMID-supported research groups that conduct drug and vaccine evaluations as part of their overall mission include the Vaccine and Treatment Evaluation Units, the International Centers for Infectious Diseases Research, the Sexually Transmitted Diseases (STD) Cooperative Research Centers, and the STD Clinical Trials Unit. In 2000, NIAID launched a phase III efficacy trial using the STD Clinical Trials Unit to determine whether azithromycin, a

drug approved for treatment of other infections, is as effective for syphilis therapy as the usual penicillin treatment; this trial continues to enroll patients. In FY 2003, NIAID launched a pivotal phase III double-blind clinical efficacy trial of an investigational vaccine for the prevention of genital herpes. This trial has expanded from 25 sites to 35 sites across the United States and is being conducted as a public-private partnership with GlaxoSmithKline, using DMID clinical sites. In addition, single-project grants and contracts support therapeutic evaluations for a number of other diseases.

Treatment-Related Research

The first step toward appropriate treatment of an infectious disease is the availability of a sensitive and specific diagnostic reagent. DMID supports many efforts to develop more effective diagnostic tools for infectious diseases. For example, DMID supports the development and manufacture of rapid, inexpensive diagnostic tests for STIs. The Division also supports research on topical microbicides, which are bactericidal or virucidal intravaginal preparations that would be used by women to prevent STIs.

In August 2004, NIAID hosted the Summit on the State of Anti-Infective Development in Bethesda, Maryland. The meeting was a followup to the Summit on Development of Infectious Disease Therapeutics, hosted by NIAID in 2000. The August summit brought together leaders from government and the pharmaceutical industry to assess the current state of antimicrobial development. A major focus of the meeting was the identification of both barriers to the development of new anti-infective agents, and opportunities for NIAID to work with the public and private sectors to help overcome those barriers.

Division of Allergy, Immunology, and Transplantation

The Division of Allergy, Immunology, and Transplantation (DAIT) supports research and

development for drugs and biologics to treat and prevent diseases mediated by the immune system, such as autoimmune diseases, primary immunodeficiencies, asthma and allergic diseases, and rejection of transplanted organs, cells, and tissues. DAIT has established several collaborative research groups to study the molecular and immunologic mechanisms that underlie the effects of immunotherapeutic agents currently being evaluated in clinical trials.

Several investigations to evaluate new and potentially more effective therapies for asthma and allergic diseases are currently underway, including immune-based therapies and the development of new medications that inhibit or stimulate specific immune system biochemical systems. DAIT-supported Autoimmunity Centers of Excellence are performing pilot clinical trials for several new immunomodulatory approaches to the prevention and treatment of autoimmune diseases. Researchers in these centers have expertise in various autoimmune diseases, including multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, and type 1 diabetes.

DAIT supports several clinical trials programs that test candidate therapies to limit immune-mediated morbidity and mortality of organ transplantation. These programs evaluate novel immunomodulatory strategies to prevent acute rejection and chronic graft loss. Strategies being examined include biological inhibitors of immune system activation, drug avoidance or minimization regimens to reduce problems associated with the immune system suppression needed to prevent rejection, and pre-transplant induction therapies to facilitate organ transplantation, prevent acute rejection, and promote immune tolerance. Through the Cooperative Clinical Trial in Pediatric Transplantation program, investigators are evaluating these strategies in children needing kidney transplants. DAIT and DAIDS cosponsor the Solid Organ Transplant in HIV program, which is implementing a multicenter prospective cohort study of kidney

and liver transplantation in people with HIV. In FY 2004, DAIT, with cosponsorship from NIDDK and the National Heart, Lung, and Blood Institute, launched the Clinical Trials in Organ Transplantation program. This cooperative, multicenter consortium will design a research agenda to address transplantation generally as an immunologic disease rather than an organ-specific disease, and will conduct clinical trials and associated mechanistic studies in pediatric and adult organ transplant recipients. In FY 2004, DAIT and NIDDK launched the Clinical Islet Transplantation program, an international consortium that will design and implement human islet transplantation studies for improved treatment of type 1 diabetes mellitus. This consortium will accelerate research in immunosuppressive therapies to prevent rejection of the transplanted islets and the underlying autoimmune disease, and develop innovative approaches to islet isolation and preservation of islet graft function.

DAIT, in collaboration with NIDDK, supports the Nonhuman Primate Transplantation Tolerance Cooperative Study Group. The goal of this program is to evaluate the safety and efficacy of new ways to induce immune tolerance of transplanted tissue, using preclinical models of kidney and islet transplantation. Scientists in this study group have demonstrated long-term graft acceptance using tolerogenic regimens in both kidney and islet allograft recipients. In FY 2002, the program was expanded from 3 to 10 research grants, which has allowed more tolerance-induction strategies to be rigorously evaluated, improved sharing of valuable resources, and helped to forge new collaborations. To further accelerate the research conducted through this program, DAIT supports breeding colonies of specific pathogen-free rhesus and cynomolgus macaques.

DAIT, with cosponsorship from NIDDK and the Juvenile Diabetes Research Foundation International, continues to support the Immune Tolerance Network (ITN). ITN is an

international consortium dedicated to the clinical evaluation of novel, tolerance-inducing therapies for autoimmune diseases, asthma and allergic diseases, and the prevention of graft rejection. The goal of tolerance-inducing therapies is to re-educate the immune system to eliminate harmful immune responses and graft rejection without reducing protective immunity to infectious agents. An important goal of ITN is to explore the immune mechanisms that cause candidate drugs to succeed or fail. ITN membership includes approximately 80 basic and clinical scientists and physicians at more than 40 institutions in the United States, Canada, Europe, and Australia.

Division of Intramural Research

Much of the research underway in NIAID's Division of Intramural Research (DIR) is intended ultimately to aid in the development of more effective therapies for infectious and immunologic diseases. Much of DIR's effort is devoted to basic studies of the immune system; disease pathogenesis; and microorganism structure, replication, and transmission. These basic studies, however, often reveal potential new therapeutic targets for treating immunologic and infectious diseases. In addition, new technologies allow more precise characterization of the activity of current drugs, which may lead to the development of more effective formulations. For example:

- DIR scientists are studying the basic mechanisms underlying the effectiveness of current TB medications. They are also integrating new methods and information from genomics and combinatorial chemistry to speed development of second-generation therapeutics-based similar modes of action. New DNA microarray-based tools for deciphering the molecular mechanisms of anti-tubercular drugs will greatly facilitate these studies²³. For additional information on TB, see the TB research section on page 121.
- Animal studies initially performed in DIR established that antibodies that bind to an immune system signaling molecule called IL-12 are an effective treatment of mucosal inflammation. Based on this finding, DIR, in collaboration with Wyeth Pharmaceuticals, participated in the development and clinical trial of a human form of the anti-IL-12 antibodies for treatment of patients with Crohn's disease. Phase I and II studies showed that the treatment is effective for active Crohn's disease, and pave the way for a phase III trial in a large patient cohort.²⁴
- DIR clinicians continued to search for less toxic treatments for an autoimmune disease called Wegener's granulomatosis (WG). In an open-label study, patients were treated for active WG first using a standardized regimen of cyclophosphamide and prednisone to drive the disease into remission, followed by mycophenolate mofetil (MMF), an immunosuppressive agent currently used in the prevention of solid organ transplant rejection for remission maintenance. The use of MMF for remission-maintenance therapy may represent a less toxic alternative for patients with WG.²⁵
- DIR scientists are developing agents to inhibit the cytokine IL-13 as a treatment for fibrosis in schistosomiasis, in which IL-13 is believed to be over-produced; other diseases in which this also occurs include asthma, idiopathic pulmonary fibrosis, and ulcerative colitis. Under a Cooperative Research and Development Agreement with Wyeth Research, the scientists plan to test several novel IL-13 inhibitors in the schistosomiasis model.²⁶

In addition to these studies, DIR scientists are conducting more than 80 clinical research protocols at the Warren Grant Magnuson Clinical Center on the NIH campus. Many of these protocols are testing the efficacy of new drug therapies developed in DIR laboratories.

EMERGING AND RE-EMERGING INFECTIOUS DISEASES

Despite remarkable advances in medical research and treatments during the 20th century, infectious diseases remain among the leading causes of death worldwide for three reasons: (1) emergence of new infectious diseases, (2) re-emergence of old infectious diseases, and (3) persistence of intractable infectious diseases. Emerging diseases include outbreaks of previously unknown diseases or known diseases whose incidence in humans has significantly increased in the past two decades. Re-emerging diseases are known diseases that have reappeared after a significant decline in incidence. Within the past two decades, innovative research and improved diagnostic and detection methods have revealed a number of previously unknown human pathogens. (For a list of emerging and re-emerging infectious diseases and pathogens, see the table below or www.niaid.nih.gov/dmid/eid/erd.htm.) Largely as a result of better detection methods, evidence also is accumulating that infective agents play a role in diseases previously thought to be chronic and noncommunicable. For example, during the past decade, chronic gastric ulcers, which formerly were thought to be caused by stress or diet, were found to be the result of infection by the bacterium *Helicobacter pylori*.

New infectious diseases continue to evolve and “emerge.” Changes in human demographics, behavior, land use, and other factors are contributing to new disease emergence by changing transmission dynamics to bring people into closer and more frequent contact with pathogens. This situation may involve exposure to animal or arthropod carriers of disease. Increasing trade in exotic animals for pets and as food sources has increased opportunities for pathogens to jump from animal reservoirs to humans. For example, close contact with exotic rodents imported to the United States as pets led to the recent outbreak of monkeypox in this country, and use of exotic civet cats for meat in China

was found to be one potential route by which the severe acute respiratory syndrome (SARS) coronavirus made the transition from animal to human hosts.

In addition to the continual discovery of new human pathogens, old infectious disease enemies are “re-emerging.” Natural genetic variations, recombinations, and adaptations allow new strains of known pathogens to appear. The immune system has not been previously exposed to these new strains and therefore is not primed to recognize them (e.g., influenza). Furthermore, human behavior plays an important role in disease re-emergence. Increased and sometimes imprudent use of antimicrobial drugs and pesticides has led to the development of resistant pathogens, allowing many diseases that were formerly treatable with drugs to make a comeback (e.g., tuberculosis, malaria, hospital-acquired and food-borne infections). Recently, decreased compliance with vaccination policy also has led to re-emergence of diseases such as measles and pertussis, which were previously under control. The use of deadly pathogens such as smallpox or anthrax as agents of bioterrorism is an increasingly acknowledged threat to the civilian population. Moreover, many important infectious diseases have never been adequately controlled on either the national or international level. Infectious diseases that have posed ongoing health problems in developing countries such as food- and water-borne infections, dengue, and West Nile virus, are re-emerging in the United States.

NIAID has developed a strategy to address the threat of emerging and re-emerging infectious diseases through targeted research and training. That strategy, which was initially outlined in the Institute’s 1996 document, *The NIAID Research Agenda for Emerging Infectious Diseases* (www.niaid.nih.gov/publications/execsum/bookcover.htm), was updated in the 2000 NIAID strategic plan, *NIAID: Planning for the 21st Century* (www.niaid.nih.gov/strategicplan/pdf/splan.pdf). In May 2001, NIAID released *NIAID Global Health Research*

Plan for HIV/AIDS, Malaria, and Tuberculosis (www.niaid.nih.gov/publications/globalhealth/global.pdf). This document outlines the Institute's plans for the next decade for diagnosing, treating, and preventing these three infections and also lays out a plan for enhancing in-country research capacity.

To an unprecedented extent, issues related to global health and infectious diseases are on the agendas of world leaders, health policymakers, and philanthropies. This attention has been focused both on scientific challenges such as vaccine development, and on the deleterious effects of infectious diseases on economic development and political stability.

To enhance the capacity to deal with the challenges posed by emerging diseases, NIAID opened a new biosafety level 3 (BSL-3) laboratory in Hamilton, Montana, in April 2002, and anticipates completion of a new BSL-3 laboratory in Rockville, Maryland. NIAID has also broken ground on a new BSL-3 laboratory on the main NIH campus in Bethesda, Maryland. These facilities will enable the Institute to conduct animal studies and laboratory research on infectious agents such as drug-resistant *Mycobacterium tuberculosis* (*M.tb*), *Borrelia*, *Yersinia*, the influenza virus, West Nile, dengue virus, and other important pathogens.

Likewise, in fiscal year (FY) 2003 NIAID established several new extramural programs to address needs for biodefense and emerging infectious disease research:

- National Biocontainment Laboratories (NBLs) and Regional Biocontainment Laboratories (RBLs). NIAID has provided funding for the construction of several new biocontainment facilities for biodefense and emerging infectious disease research: two NBLs that will provide BSL-4 research facilities (construction is expected to take up to 5 years); and nine RBLs that will provide BSL-3 research facilities (construction of these facilities is expected to take from 2 to 3 years).
- Regional Centers of Excellence (RCEs) for Biodefense and Emerging Infectious Diseases Research. Eight RCE grants were funded in September 2003, for centers located throughout the country. These RCEs are consortia of institutions usually within a region. They are funded to develop and maintain strong infrastructure and multifaceted research and development activities that will provide the scientific information and translational research capacity to make the next generation of therapeutics, vaccines, and diagnostics against the NIAID Category A, B, and C agents. Two planning grants for RCEs were funded to enable institutions to develop consortia for the study of these pathogens and to support research program initiation and resource acquisition.
- NIAID's Biodefense and Emerging Infections Research Resources Program supports the acquisition, authentication, storage, and distribution to the scientific community of state-of-the-art research and reference reagents related to biodefense and emerging infectious diseases. Included are the capability to validate, expand, and produce biological agents, including cell lines, clones, proteins, monoclonal and polyclonal antibodies, and diagnostic tools.
- Contracts funded under the *In Vitro* and Animal Models for Emerging Infectious Diseases and Biodefense program provide a range of resources for preclinical testing of new therapies and vaccines, including nonhuman primate models. Under these new contracts, task orders for small animal and nonhuman primate models for anthrax are being developed and validated for Food and Drug Administration (FDA) licensure of vaccines and therapeutics against inhalational anthrax. Included in this activity are safety,

toxicology, and pharmaceutical testing in small and large animals, including the capability for conducting challenge studies. Future task order awards will develop, validate, and use models for other Category A, B, and C pathogens.

- The Food and Waterborne Diseases Integrated Research Network expands the Institute's capacity to conduct clinical research studies of food- and water-borne enteric pathogens. Through one of the Microbiology Research Units with a botulism research center, NIAID is determining the pharmacokinetics of botulinum toxins and antitoxins in several animal models. These data are helpful for the development, formulation, and use of equine-based antitoxins and will serve as a basis for next-generation antitoxins.

Basic and clinical research is critical to the development of a national strategy to confront these microbial challenges. Such research increases our collective understanding of ever-changing microbial populations and permits this new knowledge to be transformed into better diagnostics, vaccines, and therapies. Basic research and research training also are the foundation for surveillance and response activities.

During 2004, NIAID supported research initiatives on biodefense as well as on emerging and re-emerging infectious diseases in multiple areas, including SARS, influenza, TB, and other infectious diseases and deadly pathogens.

List of NIAID Emerging and Re-emerging Diseases 2004

Group I—Pathogens Newly Recognized in the Past Two Decades

Acanthamebiasis
 Australian bat Lyssavirus
 Babesia, atypical
Bartonella henselae
 Coronaviruses/Severe Acute Respiratory Syndrome (SARS)
 Ehrlichiosis
Encephalitozoon cuniculi
Encephalitozoon hellem
Enterocytozoon bieneusi
Helicobacter pylori
 Hendra or equine morbilli virus
 Hepatitis C
 Hepatitis E
 Human herpesvirus 8
 Human herpesvirus 6
 Lyme borreliosis
 Microsporidia
 Parvovirus B19

Group II—Re-emerging Pathogens

Coccidioides immitis
 Enterovirus 71

Prion diseases
Streptococcus, group A
Staphylococcus aureus

Group III—Agents with Bioterrorism Potential

■ CDC—Category A

Bacillus anthracis (anthrax)
Clostridium botulinum
Francisella tularensis (tularemia)
Variola major (smallpox) and other pox viruses
 Viral hemorrhagic fevers
 Arenaviruses
 LCM, Junin virus, Machupo virus, Guanarito virus
 Lassa Fever
 Bunyaviruses
 Hantaviruses
 Rift Valley Fever
 Flaviruses
 Dengue
 Filoviruses
 Ebola
 Marburg
Yersinia pestis

List of NIAID Emerging and Re-emerging Diseases 2004

■ CDC—Category B

Brucella species (brucellosis)
Burkholderia pseudomallei (melioidosis)
Burkholderia mallei (glanders)
Coxiella burnetii (Q fever)
 Epsilon toxin of *Clostridium perfringens*
 Food-borne and Water-borne Pathogens

Bacteria

Campylobacter jejuni
 Diarrheagenic *E. coli*
Listeria monocytogenes
 Pathogenic vibrios
Salmonella
Shigella species
Yersinia enterocolitica

Protozoa

Cryptosporidium parvum
Cyclospora cayatanensis
Entamoeba histolytica
Giardia lamblia
 Microsporidia
 Toxoplasma

Viruses (calciviruses, hepatitis A)

Additional viral encephalitis

California encephalitis

Eastern equine encephalitis

Japanese encephalitis virus

Kyasanur Forest virus

LaCrosse virus

Venezuelan equine encephalitis

Western equine encephalitis

West Nile virus

Ricin toxin (from *Ricinus communis*)

Staphylococcal enterotoxin B

Typhus fever (*Rickettsia prowazekii*)

■ CDC—Category C

Emerging infectious disease threats such as Nipah virus, additional hantaviruses, and the following pathogens:

Influenza

Other rickettsias

Multidrug-resistant tuberculosis (MDR-TB)

Rabies

Severe acute respiratory syndrome-associated coronavirus (SARS-CoV)

Tick-borne encephalitis viruses

Tick-borne hemorrhagic fever viruses

Crimean-Congo hemorrhagic fever virus

Yellow fever

Pathogens that naturally emerge with, or are engineered for, increased virulence, increased transmission, and/or the ability to evade the immune response.

Emerging and Re-emerging Infectious Diseases

Severe Acute Respiratory Syndrome—SARS

In the spring of 2003, the world became aware of an outbreak of a newly recognized pneumonia that was named “severe acute respiratory syndrome,” or SARS. The outbreak is thought to have begun in southeastern China’s Guangdong province in November 2002, with subsequent spread to the special administrative region of Hong Kong by February 2003. Significant outbreaks also occurred in other Asian countries such as Vietnam and Singapore, and in Canada. Epidemiologic investigation showed that the disease disproportionately affected healthcare workers and other close contacts of patients

such as family members. Through an NIAID-supported contract with Dr. Robert Webster at St. Jude Children’s Research Hospital in Memphis, researchers at Hong Kong University and their colleagues at four local hospitals were the first to report to the World Health Organization (WHO) the isolation of a virus that was linked conclusively to SARS patients. Using a high-powered microscope, researchers examined a culture from a lung biopsy sample and found virus particles whose surface was studded with an array of proteins resembling a crown around the virus—a “coronavirus.” The researchers then used antibody tests and other molecular tools to confirm that this deadly coronavirus was present in at least 35 of the SARS patients they were studying.

Before the emergence of SARS (also called SARS-CoV), human coronaviruses were predominately associated with up to 30 percent of common colds. Coronaviruses are the largest single-stranded RNA viruses known and are divided into three serogroups. Recent data indicate that SARS is the prototype strain for a new fourth group of coronaviruses.

In response to the need for rapidly increased research on the SARS coronavirus, in FY 2003, NIAID awarded administrative supplements to grantees to expand activities on the basic biology and immunology of coronaviruses. Currently, NIAID administers more than 20 grants to support basic research on animal coronaviruses and more than 25 grants on SARS. NIAID also supports contracts to develop diagnostics, vaccines, and therapeutics for SARS. In addition, NIAID supports epidemiologic work on SARS and conducts SARS research within its intramural program. Highlights include:

- NIAID Division of Intramural Research (DIR) scientists and their collaborators developed a mouse model of SARS replication that allows the evaluation of vaccines, immunotherapies, and antiviral drugs. Using the model, the scientists demonstrated that mice produce neutralizing antibodies to the SARS virus that protect the mice from re-infection. In addition, transfer of immune sera from infected mice protected other mice from SARS infection. These observations suggest that vaccines that induce neutralizing antibodies and strategies for immunoprophylaxis or immunotherapy are likely to be effective in SARS. Since its development, the mouse model has been used to demonstrate the efficacy of a DNA vaccine, an inactivated vaccine, a vectored vaccine, and three candidate immunotherapies.²⁷
- To date, NIAID screening contracts have evaluated more than 20,000 chemicals for anti-SARS-CoV activity. These NIAID-supported investigators have screened more than 1,400 compounds, including all FDA-approved antiviral drugs. Four compounds, thus far, have shown activity and will be studied further.
- NIAID awarded five contracts, grants, and supplements to companies and researchers towards development of vaccines for SARS, covering a variety of different vaccine approaches.
- NIAID-supported researchers at Hong Kong University have developed a polymerase chain reaction assay for detection of the SARS coronavirus. The test has been shown to detect the SARS virus in respiratory aspirates and fecal samples.
- NIAID is supporting the development of a diagnostic microarray that will be able to detect influenza, SARS, and other respiratory viruses.
- NIAID has expanded its Pandemic Preparedness in Asia contract with St. Jude Children's Research Hospital (Dr. Robert Webster, Principal Investigator) to:
 - Expand efforts to identify the animal reservoirs for coronaviruses in Asia;
 - Establish cell-based laboratory assays to assess the immune response in infected patients; and
 - Conduct seroepidemiologic studies of family members and other close contacts of SARS patients to assess the rates of asymptomatic infections.
- NIAID is supporting the generation and distribution of a variety of SARS reagents for the research community, including:
 - **Overlapping peptides.** The NIH AIDS Research and Reference Reagent Program developed important tools for researchers to help understand the

immune response to the SARS virus. One of these tools, a set of synthetic overlapping peptides covering the N, M, and S genes of the SARS virus, can be used to map the T cell responses in exposed and infected people. Use of these peptides will help to determine whether SARS patients with different disease outcomes have quantitatively different T cell responses to viral proteins.

- **SARS microarrays.** NIAID's Pathogen Functional Genomics Resource Center has developed microarrays that contain genetic sequences of SARS coronavirus isolates from the United States, Canada, and Asia, which can be used to detect tiny genetic variations in the SARS viruses. With this information and information on the clinical outcomes of patients infected with SARS, scientists hope to determine which strains are most dangerous and to gain information on the development of antiviral drugs.
- In preparation for the re-emergence of SARS, NIAID is developing a clinical protocol to evaluate Interferon alfacon-1 (INFERGEN), an engineered recombinant interferon molecule that has potent anti-SARS-CoV activity in an *in vitro* assay (cytopathic effect). NIAID's Collaborative Antiviral Study Group is leading these efforts, in consultation with the Centers for Disease Control and Prevention (CDC) and colleagues from Toronto.
- NIAID issued a number of solicitations for grant and contract proposals to further expand research on SARS and accelerate product development. These new programs include development of diagnostics, vaccines, and therapeutics for SARS and will provide opportunities for partnerships between academia, government, and the private sector.

For more information on SARS research updates and opportunities, please visit www.niaid.nih.gov/dmid/sarsapps.htm and www.niaid.nih.gov/factsheets/sars.htm.

West Nile Virus

NIAID supports a robust West Nile virus research portfolio. The following points summarize key research in several different areas:

- NIAID conducts basic research, which leads to a better understanding of the host, pathogen, and environmental factors that influence disease emergence. Basic research determines which flavivirus proteins contribute to the virus's ability to cause disease and examines how protective immune responses are elicited within the central nervous system during acute flavivirus encephalitis.
- A golden hamster model has been developed by NIAID-supported researchers and is used for screening drugs and for examining factors that contribute to immunity. This model has proven useful in evaluating strategies for



Researcher wearing biosafety gear to demonstrate preparation of infected tissue culture plates.

preventing the complications associated with this emerging infectious disease.

- In 1999, NIAID funded a fast-track project to develop a candidate West Nile virus vaccine with Acambis, Inc. Since then, scientists have developed a prototype vaccine and conducted initial feasibility studies. The vaccine is a chimeric vaccine (West Nile virus protein on a yellow fever vaccine). The Acambis West Nile virus vaccine candidate has so far demonstrated good safety, efficacy, and protection against disease in animal models. Phase I clinical trials in humans began in November 2003 by Acambis.
- A DNA vaccine is being supported by NIAID. A phase I clinical trial is planned for early 2005.
- NIAID has funded investigators to establish a system to screen chemical compounds for possible antiviral activity against West Nile virus. More than 1,000 compounds have been screened, and several have moved forward to preclinical evaluation. NIAID also is supporting research on immunotherapeutics.
- NIAID supports the World Reference Center for Arboviruses, which has reference anti-West Nile sera and seed lots of various strains of West Nile virus. These reagents were provided when requested by investigators in the United States and Canada.
- At the end of FY 2002, the Division of Microbiology and Infectious Diseases (DMID) awarded two contracts to establish Emerging Viral Diseases Centers in response to a Request for Proposals titled "U.S. Based Collaboration in Emerging Viral and Prion Diseases." Each contract establishes broad-based, interactive, multidisciplinary research teams with the scientific expertise needed to study the emergence of a wide variety of zoonotic and arthropod-borne viral pathogens and other emerging viral

threats. Both contracts also provide capacity to redirect funds and resources in the event of an urgent public health threat from either natural disease or bioterrorist release. Under this provision, research on the newly discovered SARS coronavirus is being conducted at both sites. These contracts cover several important areas of research, including basic biology of the virus, West Nile virus ecology and pathogenic/epidemic potential, diagnosis, prevention, and therapy.

- NIAID supports research aimed at better understanding the vectors of transmission in affected areas. Such an understanding will allow improved monitoring and surveillance for the vectors and the viruses they transmit. NIAID also supports the development and preliminary testing of vector control strategies.
- NIAID intramural scientists also have developed a West Nile virus vaccine candidate, which they have tested in monkeys and horses with promising results. This vaccine candidate is a result of groundbreaking studies conducted more than a decade ago, in which NIAID scientists combined parts of different flaviviruses (a family of viruses that includes West Nile virus, dengue, Japanese encephalitis, and others) to make them weaker and thus more suitable for a live-virus vaccine. The West Nile virus vaccine uses part of the dengue virus as a backbone to which protective antibody-eliciting components of the West Nile virus are added. A supply of this vaccine suitable for human use has been prepared, and phase I human trials are planned for 2005. Development of other vaccine approaches, such as a full-length cDNA-derived West Nile virus vaccine, is under way.

For more information on West Nile virus and NIAID's research portfolio in this area, see www.niaid.nih.gov/publications/wnile/default.htm and www.niaid.nih.gov/factsheets/westnile.htm.

Tuberculosis

M.tb kills more people globally than any other single infectious agent. It is estimated that one-third of the world's population (1.86 billion people) is infected with *M.tb*, and 16.2 million people currently have tuberculosis (TB).²⁸ In 2002, an estimated 8.8 million persons developed TB, and 2 million patients died from this disease. Based on these statistics, TB kills more adults globally than any other single infectious agent.²⁹

The majority of TB cases occur in developing nations. Although TB is essentially a treatable disease, lack of availability of drugs in many countries, poor adherence to treatment schedules due to side effects, and the long duration of treatment (6 to 12 months) have resulted in the development of single drug-resistant and multidrug-resistant TB (MDR-TB) strains producing TB that is much more difficult to cure. Furthermore, the link between HIV and TB is believed to be a major factor in the spread of TB. In 1997, of the 1.86 billion individuals worldwide who were infected with *M.tb*, approximately 10.7 million also were infected with HIV. In Africa, TB cases are increasing by 10 percent each year because of HIV. These factors, combined with a suboptimal public health infrastructure in many countries, contribute to the ongoing spread and re-emergence of TB worldwide.

NIAID TB research efforts are carried out through a comprehensive extramural and intramural program funding all aspects of basic, translational, and applied research leading to a better understanding of TB as an infection and disease, as well as to the development of novel vaccines, drugs, and diagnostics. Research on TB is an important part of NIAID's global health portfolio, as is articulated in the NIAID Global Health Research Plan for HIV/AIDS, Malaria, and Tuberculosis (<http://www.niaid.nih.gov/publications/globalhealth/global.pdf>). Highlights of the NIAID TB research program include:

- **Basic biology.** NIAID supports basic research on the disease-causing mechanisms

of the bacteria, as well as host immune responses to mycobacterial infection, including the identification of potential targets that might be used in vaccination or treatment of the disease.

- **Drug discovery and evaluation.** NIAID supports the evaluation of new candidate antibiotics against virulent *M.tb* in laboratory assays and in animal models of disease (see <http://www.taacf.org>). The Institute also supports research to determine mechanisms of drug resistance and activity, early target identification and verification, and clinical testing of prophylactic and therapeutic anti-TB regimens.
- **Vaccine development and evaluation.** NIAID supports basic and clinical research leading to the development and testing of effective new vaccines for the prevention and control of TB.
- **Public/private partnerships.** NIAID works closely with industry to merge basic science with industry expertise in the development of TB therapeutics and vaccines. NIAID supports these efforts through the award of Challenge Grants, cooperative agreements, and small business grants, as well as participation in public-private partnerships.

Lyme Disease

Lyme disease (borreliosis) is the most prevalent tick-borne infectious disease in the United States. In 2003, the CDC reported 21,273 cases throughout the United States.³⁰ Five states—New York, Pennsylvania, Massachusetts, Connecticut, and New Jersey—accounted for 80 percent of all reported cases.³¹

The major goals of the NIAID Lyme disease research program are to develop better means of diagnosing, treating, and preventing this disease. To accomplish these objectives, the NIAID Lyme disease research portfolio includes a broad range of activities that are essential to

increasing our understanding of the disease. The studies include both intramural and extramural research on animal models of disease, microbial physiology, molecular and cellular mechanisms of pathogenesis, mechanisms of protective immunity, vectors and disease transmission, efficacy of different modes of antibiotic therapy, and development of more sensitive and reliable diagnostic tests for both early (acute) and late (chronic) Lyme disease.

NIAID intramural investigators are studying Lyme disease on the NIH campus in Bethesda, Maryland, and at the Rocky Mountain Laboratories (RML) in Hamilton, Montana, where NIAID scientists discovered the etiologic agent *Borrelia burgdorferi* in the early 1980s.³² RML scientists are using microarray technology to identify genes associated with unique aspects of the pathogenicity of Lyme disease and other relapsing fever microorganisms. In addition, working with members of the California Department of Health Services, RML researchers identified two new areas in California where a tick-borne relative of the Lyme disease bacterium called *Borrelia hermsii* has been found to cause relapsing fever. This finding will help alert the medical community and public health workers about the potential for this tick-borne disease to be acquired in these areas.

On the NIH campus, NIAID clinical investigators seek to better understand the natural history of chronic Lyme disease and possible causes for persisting symptoms. To this end, two clinical studies currently are ongoing at the NIH Clinical Center: one to evaluate and treat patients with classic Lyme disease, and the other to conduct a comprehensive clinical, microbiologic, and immunologic assessment of patients who have suspected chronic Lyme disease despite previous antibiotic therapy. In addition, NIAID clinical scientists are collaborating with colleagues to further evaluate C6 peptide enzyme-linked immunosorbent assay (ELISA), which can detect infection with both the U.S. and European strains of *Borrelia*, and can be used to diagnose Lyme

disease in patients who have received the Lyme disease vaccine.

NIAID also supports an FY 2003 research initiative titled Partnerships for Hepatitis B and Vector-Borne Diseases. This initiative is an expansion of previous efforts that targeted animal vectors of disease and fostered development of partnerships among government, academia, and the biotechnology and pharmaceutical industries. NIAID funded two grants on Lyme disease immunology and vaccine development under the 2003 initiative.

Lyme borreliosis and ehrlichiosis will continue to be areas of high priority for basic research for NIAID, especially with regard to: (1) the characterization and treatment of acute and chronic infection; (2) the influence of co-infection with other vector-borne pathogens on the diagnosis, treatment, and severity of Lyme disease; and (3) the development of rapid, sensitive, and specific diagnostic tests and preventive strategies (e.g., vaccines and vector control measures).

Influenza

In the United States, pneumonia and influenza are the seventh leading cause of death, responsible for 2.7 percent of all deaths.³³ Research supported by NIAID has led to many new insights about how influenza causes disease.

The major goal of the NIAID influenza program is to support research leading to more effective approaches to control influenza virus infections. NIAID currently supports research in the following major areas:

- **Basic biology.** NIAID supports basic research on virus structure and function, viral pathogenesis, and the host response to infection.
- **Surveillance/epidemiology.** NIAID supports research to better understand the natural history and emergence of influenza

viruses with pandemic potential and to evaluate community-based strategies for interrupting the spread of influenza.

- **Public/private partnerships.** In 2000, NIAID awarded three challenge grants (requiring matching funds) to private-sector companies for the development of new vaccines against pandemic influenza strains. These companies are using live-attenuated viruses, virus-like particles, tissue culture substrates, and reverse genetics strategies to rapidly produce high-growth viruses for vaccine production. In 2003 and 2004, NIAID awarded multiple cooperative agreements to private sector companies/academic collaborators to develop new countermeasures against influenza virus.
- **Drug discovery and evaluation.** NIAID supports the development of novel drugs against influenza and the evaluation of these new agents in both *in vitro* screening assays and animal models. In 2004, NIAID screened more than 170 compounds.
- **Vaccine development and evaluation.** Developing new influenza vaccines and strategies has been a major focus of the NIAID influenza program. These strategies include supporting the development of live-attenuated and recombinant vaccines, immunomodulators and adjuvants, cell culture-based vaccines, and basic research aimed at optimizing the immune response. NIAID also supports the production of pilot lot vaccines against avian influenza subtypes of high pandemic potential.

In 2003, FDA approved FluMist, a new intranasally administered influenza vaccine. NIAID supported the development of this vaccine for more than 30 years, through both its intramural program and extramural contracts and cooperative research and development agreements (CRADAs). Since the 1970s, NIAID has supported studies to evaluate the safety and

immunogenicity of strains of the influenza virus that replicate only in the upper respiratory tract (temperature sensitive) and cause only minimal symptoms (attenuated), which could therefore be used as vaccines. In 1995, NIAID entered into a CRADA with Aviron for the commercialization of the product. Over the past 8 years, NIAID has conducted a series of clinical trials to evaluate the vaccine in children and in HIV-positive adults and children. In June 2003, FDA approved FluMist for healthy children and adults aged 5 to 49 years. The potential advantages of FluMist include the ease of administration and the ability to induce a broad immune response.

In addition, NIAID's intramural program is developing vaccines against potential pandemic influenza strains. An optimal public health response in the event of a potential pandemic requires that vaccines be available with minimum delay. NIAID intramural scientists and colleagues from CDC have initiated a collaborative, proactive approach to pandemic preparedness. They plan to generate and evaluate up to two dozen candidate vaccines against influenza A subtypes that are recognized to have pandemic potential. Using classic genetic recombination techniques, the team has developed a candidate inactivated H9N2 vaccine that has demonstrated efficacy in preclinical testing. Clinical studies of this candidate vaccine are planned for 2005. In addition, the scientists have engineered live-attenuated vaccine candidates against the 1997, 2003, and 2004 H5N1 avian viruses. In 2004, the H5N1 virus killed 31 of 43 humans known to be infected as of October 4th.³⁴

In 2003, NIAID also expanded its Pandemic Preparedness in Asia contract with St. Jude Children's Research Hospital in Memphis. (The original award was made in 1998 for the surveillance and characterization of avian influenza viruses with pandemic potential in the live bird markets in Hong Kong.) Activities conducted under this expansion include establishing animal influenza surveillance sites in Asia, generating high-yield vaccine candidates

against influenza strains with pandemic potential and accompanying reagents, supporting an international animal surveillance training course in Hong Kong (March 2004), and studying newly emerging influenza strains infecting swine in the United States.

The major focus of the NIAID influenza program will continue to be on basic and applied research that promises to further the development of new and improved vaccines and antiviral agents.

For more information on influenza, including weekly reports on flu activity, go to www.cdc.gov/flu/weekly/fluactivity.htm.

Prion Diseases

NIAID's DIR has a productive and growing program focused on transmissible spongiform encephalopathies (TSEs). These diseases also are called "prion diseases" because they are believed to be caused and transmitted by prion proteins, a new type of infectious agent discovered in the 1980s. Prion proteins enter cells and cause normal cellular proteins to adopt abnormal three-dimensional structures, which in turn leads to disease. TSEs are fatal neurodegenerative diseases and include scrapie, Creutzfeldt-Jakob disease (CJD), bovine spongiform encephalopathy (BSE or "mad cow" disease), and chronic wasting disease (CWD) of deer and elk. Since the onset of the BSE epidemic in the United Kingdom in the 1980s, the disease has resulted in the destruction of millions of animals in Europe. Because the BSE epidemic was temporally and geographically associated with the emergence of a variant form of CJD in humans, health officials believe the disease was spread to humans by infected beef. In May 2003, the finding of BSE in a single cow in Canada resulted in a ban on exportation of certain live ruminants and ruminant products from Canada to the United States.

NIAID's intramural TSE research is aimed at increasing fundamental understandings of prion protein (PrP) and the mechanisms responsible for

the accumulation in nervous system cells of the abnormal form of PrP, which appears to underlie TSE pathogenesis. Studies also are ongoing to elucidate the mechanisms of cross-species transmission of TSE disease. This work is highly important in light of the epidemiology of variant CJD as well as the discovery of CWD in deer and elk herds beyond the areas in the western United States in which it was long known to exist. DIR scientists have conducted experiments that suggest that species once thought to be resistant to certain TSE strains can serve as lifelong carriers of the infection without ever becoming sick. Infrastructure improvements at NIAID's RML, including construction of new BSL-3 laboratory and animal facilities, have allowed expansion of TSE transmission studies. An important study to determine whether CWD PrP can be transmitted to nonhuman primates via oral or intracerebral routes has begun, using CWD samples obtained through NIAID's collaboration with the Wyoming Department of Health.

DIR scientists also have developed a high-throughput screening method to find compounds that show promise as potential TSE therapeutics. Studies of the potential use of antibody and other vaccine-based therapies for TSEs are ongoing in NIAID laboratories. In addition, to advance earlier peptide studies, novel PrP peptides have been synthesized and are being evaluated for their ability to block the conversion of normal PrP to abnormal PrP *in vitro*. PrP peptides dispensed by direct injection or delivered by gene therapy might provide specific therapeutic treatment for TSE diseases. Promising compounds will be evaluated *in vivo* through a DMID contract with Utah State University. (See below.)

NIH provides grant support for investigator-initiated studies of CWD transmission that seek to better understand prion entry, trafficking, and neuroinvasion in the lymphoid system, which could provide a basis for development of diagnostic and intervention strategies. In addition, NIH has taken a number of actions in

response to the Department's 2001 BSE/TSE Action Plan, including:

- NIAID awarded a 7-year, \$8.4 million contract to Colorado State University to establish an emerging disease research center focused on CWD. Researchers at the center will isolate, identify, and characterize strains of CWD; evaluate the potential for both inter- and intraspecies transmission; study the pathogenesis of CWD; perform preclinical, animal model-based evaluation of newly developed prevention measures or therapies for CWD; develop, analyze, and distribute reagents, infectious material, molecular clones, and transgenic mice to the research community; and implement a systematic approach to furthering understandings of the ecologic and environmental factors influencing the emergence, spread, and distribution of CWD and of the basic epidemiology and clinical aspects of these diseases.
- NIH is evaluating potential anti-TSE compounds in animal models. Through expansion of an NIAID contract with Utah State University, candidate compounds are evaluated for efficacy in transgenic animals that have a shortened time to death. This model was established at Utah State in collaboration with NIAID's RML.

GENOMICS

Division of Microbiology and Infectious Diseases

The Division of Microbiology and Infectious Diseases supports a substantial program in genomics research, including sequencing of human pathogens and invertebrate vectors of diseases, applying genomic and proteomic technologies to the study of microorganisms and infectious diseases, supporting genomic databases, and providing high-quality genomic technological resources to the scientific community.

Genome Sequencing

A genome is an organism's complete set of genes, encoded as a specific sequence of paired DNA bases. Recent advances in molecular biology have given researchers powerful methods that can quickly and accurately determine the complete DNA sequence of the whole genome of virtually any organism, including disease-causing microorganisms and the insect and other invertebrate vectors that can transmit them.

Whole-genome sequencing is an enormously powerful tool for understanding and defeating infectious diseases. For example, scientists can compare and contrast genomes to identify genes that are unique to a particular microbe. They can then target these genes with specific drugs, incorporate the products of these genes into experimental vaccines, and develop more sensitive diagnostic tests. Moreover, sequence information can reveal small genetic variations between different strains of a given pathogen. Researchers can use these subtle differences to determine which genes affect a pathogen's virulence, which genes are involved in the development of antibiotic resistance, and how a virulent or resistant strain spreads within a susceptible population; better understanding of these phenomena will help to improve disease diagnosis and patient care. Finally, understanding how microbial genes interact with one another

and the human host during infection will lead to new strategies for drug therapies and vaccine development.

To capitalize on the tremendous potential of genome sequencing, NIAID has invested heavily in projects to sequence the genomes of medically important microbes. Sequencing technology has advanced to the point where NIAID working alone can fund the determination of a bacterial species; however, NIAID collaborates with other funding agencies to sequence the larger genomes of protozoan and fungal pathogens. In total, NIAID has supported 57 genome-sequencing projects for 45 bacteria, 3 fungi, 8 parasitic protozoa, and 1 invertebrate vector of disease. The bacterial species include those that cause anthrax, plague, tuberculosis, gonorrhea, chlamydia, cholera, strep throat, scarlet fever, and food-borne diseases. DNA sequencing projects have also been completed for protozoan parasites *Cryptosporidium parvum*, *Entamoeba histolytica*, *Toxoplasma gondii*, and *Trypanosoma brucei* and the fungi *Aspergillus fumigatus* and *Cryptococcus neoformans*. NIAID's data release policies ensure that both raw genome sequence data and associated annotations are available to scientists around the world through publicly accessible databases. A list of NIAID-supported large-scale pathogen genome-sequencing projects is provided on page 89.

Study of the genomics of malaria has been particularly successful; for the first time, researchers have in hand the complete genetic sequences of the infectious organism, its natural host, and the insect that transmits it. In 2002, the International Malaria Genome Sequencing Consortium—funded in part by NIAID—published the genome sequence of *Plasmodium falciparum*, the parasite that causes the most severe form of malaria. NIAID also supported the rapid sequencing of the genome of *Anopheles gambiae*, the mosquito that transmits the malaria parasite to humans. Researchers therefore now have the genome sequences of all three organisms involved in malaria—the mosquito vector, the

malaria parasite, and the human host. This has provided scientists with a unique opportunity to unravel the complex interactions between these three species on a molecular level. Indeed, NIAID-supported scientists already have taken advantage of this valuable genomic information to gain new insights into the molecular mechanisms involved in insecticide resistance and to identify genes and gene products that are promising targets for new drug therapies.

The national biodefense effort has benefited substantially from genomic research as well, and NIAID has made a significant investment in sequencing microorganisms with the highest priority as agents of bioterrorism. For example, NIAID collaborated with the Office of Naval Research and the Department of Energy to sequence the genome of the Ames strain of *Bacillus anthracis*, the bacterium that causes anthrax. Other organisms important to biodefense that NIAID has helped to sequence include *Brucella suis*; *Burkholderia mallei*; *Clostridium perfringens*; *Coxiella burnetii*; and *Rickettsia typhi*; *Staphylococcus aureus*; *Yersinia pestis*; *Mycobacterium tuberculosis*; food-borne bacterial pathogens including *Escherichia coli*, *Vibrio cholerae*, *Shigella*, and *Salmonella*; and parasitic protozoa including *Cryptosporidium parvum*, *Giardia lamblia*, *Entamoeba histolytica*, and *Toxoplasma gondii*.

Because anthrax is a particularly dangerous bioterror agent, NIAID has expanded its sequencing efforts for *Bacillus anthracis* and has developed a comprehensive genomic analysis that includes sequencing of additional strains, clinical isolates, near neighbors, and related species. Under this expansion, sequencing projects were completed for six *Bacillus anthracis* strains and for two strains of the closely related bacterium *Bacillus cereus*. This effort has provided biomarkers to facilitate forensic strain identification; furthered the understanding of microbial pathogenesis; and facilitated the discovery of new targets for drugs, vaccines, and diagnostics to combat an anthrax attack.

Genomic Research

Obtaining the raw sequence of an organism's genome is only the first step in understanding it; annotating and organizing the sequence data are also required. Furthermore, the sequence data allow researchers to study an organism's proteome—the entire set of proteins that are encoded in the genome sequence. NIAID-supported investigators are applying such emerging genomic technologies to study microorganisms and infectious diseases. These studies include both basic research topics, such as the biology of a pathogen and the host's response to infection, and applied research such as development of medical diagnostics, drugs, and vaccines. Genomic technologies help scientists study infectious agents at the whole genome or proteome level. For example:

- Whole genome and proteome expression studies are being used to identify pathogen-specific genes and proteins involved in virulence, pathogenesis, and disease transmission.
- Proteomic technologies are being applied to both the pathogen and the host proteome to allow identification of candidate protein targets for the new vaccines, therapeutics, and diagnostics.
- Genomic technologies are providing platforms for examination of genetic variation within and between species, strains, and clinical isolates, as well as for study of host responses to infection, vaccines, and antibiotic drugs.

Genomic Resources, Reagents, and Technologies

NIAID facilitates distribution of genomic resources and technologies to the research community for functional genomic analysis of microbial pathogens and supports the development of bioinformatic and computational

tools that allow investigators to store and manipulate genomic and postgenomic data.

NIAID continues to support the Pathogen Functional Genomics Resource Center (PFGRC) at The Institute of Genomic Research (TIGR) in Rockville, Maryland. PFGRC was established in 2001 to distribute to the research community a wide range of genomic and related resources and technologies for the functional analysis of microbial pathogens and invertebrate vectors of infectious diseases. Considerable progress has been made toward this goal, including the generation and distribution to the research community of 19 organism-specific microarrays. This includes arrays for *Aspergillus fumigatus*, *Chlamydia*, human SARS chip, *Helicobacter pylori*, *Coronavirus* (animal and human), *Mycobacterium smegmatis*, *Mycobacterium tuberculosis*, *Neisseria gonorrhoeae*, *Plasmodium falciparum*, *Salmonella typhimurium*, *Staphylococcus aureus*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, and *Trypanosoma cruzi*.

The mission of PFGRC has been expanded to provide the research community with resources and reagents to conduct both basic and applied research on microorganisms with a high potential to be used as agents of bioterrorism, and has generated and distributed organism-specific microarrays for *Bacillus anthracis*, *Clostridium botulinum*, *Listeria monocytogenes*, *Vibrio cholerae*, and *Yersinia pestis*. In addition, microarray technology developed by Affymetrix, Inc., was added to PFGRC, and new genomic software tools have been developed for comparative genomics. PFGRC has provided severe acute respiratory syndrome (SARS) genomic resources to the broad scientific community to spur basic and applied research on SARS. PFGRC has also developed methods for generating organism-specific protein expression clones for human SARS coronavirus, *Bacillus anthracis*, *Vibrio cholerae*, and *Mycobacterium tuberculosis* and other pathogens. Further information is available at www.niaid.nih.gov/dmid/genomes/pfgrc/default.htm.

In FY 2003, NIAID awarded a contract to TIGR to support a Microbial Genome Sequencing Center to allow for rapid and cost-efficient production of high-quality, microbial genome sequences; in early FY 2004, NIAID awarded a contract to Massachusetts Institute of Technology to support a similar sequencing center. Genomes to be sequenced include microorganisms considered agents of bioterrorism (NIAID Category A, B, and C agents), microorganisms responsible for emerging and re-emerging infectious diseases, related pathogens, clinical isolates, and invertebrate vectors of infectious diseases. These sequencing centers have the capacity to respond to national needs and government priorities for genome sequencing, filling in sequence gaps and thus providing genome sequencing data for multiple uses, including forensic strain identification and identification of targets for drugs, vaccines, and diagnostics. In FY 2004, NIAID supported new genome sequencing projects for additional strains of *Burkholderia mallei*, *Burkholderia pseudomallei*, coronaviruses, pathogenic *E. coli*, *Francisella tularensis*, *Influenza*, *Mycobacterium tuberculosis*, *Shigella*, *Vibrio cholerae*, and *Yersinia pestis*. In addition, NIAID approved sequencing projects for invertebrate vectors of infectious diseases, *Aedes aegypti*, *Culex pipiens*, and *Ixodes scapularis*. Further information can be found at www.niaid.nih.gov/dmid/genomes/mscs.

The Malaria Research and Reference Reagent Resource (MR4) Center (www.malaria.mr4.org) continued to provide expanded access to quality-controlled reagents for the international malaria research community in 2004.

Bioinformatics and Databases

NIAID has awarded several contracts to establish Bioinformatics Resource Centers. These centers will develop, populate, and maintain comprehensive relational databases to collect, store, display, annotate, query, and analyze genomic, structural, and related data for emerging and re-emerging pathogens, including those

important for biodefense. The centers will also develop and provide software tools to assist in data analysis. Eight centers were funded in FY 2004. The databases these centers maintain are a valuable genomic resource, providing the scientific community with easy access to large amounts of genomic and related data and bioinformatics tools for data analysis. Further information is available at <http://www.niaid.nih.gov/dmid/genomes/brc/default.htm>.

Genomics and Proteomics

NIAID awarded contracts for Biodefense Proteomics Research Programs: Identifying Targets for Therapeutic Interventions Using Proteomic Technology. The goals of this program are to develop and improve proteomic technologies, and to apply these technologies to pathogen and host cell proteomes for the discovery and identification of novel targets for the next generation of drugs, vaccines, diagnostics, and immunotherapeutics against microorganisms considered agents of bioterrorism. Seven centers have been funded to date; they focus on a range of NIAID category A–C biodefense agents. Further information is available at www.niaid.nih.gov/dmid/genomes/prc/default.htm.

NIAID continues to collaborate with the National Institute of General Medical Sciences (NIGMS) on the NIGMS Protein Structure Initiative, which supports research centers for the development of high-throughput methods and structural determination of proteins; further information can be found at www.nigms.nih.gov/psi. One project supports the determination and analysis of structures of more than 400 functionally relevant *Mycobacterium tuberculosis* proteins, and another project focuses on determining the protein structures from pathogenic protozoa. Structural and functional information on many proteins from this pathogen is now available in Web-based databases for access by the scientific community at www.sgpp.org and www.doe-mbi.ucla.edu/TB.

Division of Allergy, Immunology, and Transplantation

The Division of Allergy, Immunology, and Transplantation (DAIT) also supports genomics research. The human immune system is composed of complex networks of interacting cells, each programmed by precisely scripted genes. Underlying each immune response to a disease is a multistep pathway of interacting molecules influenced by an individual's unique genomic characteristics. The immune system plays a critical role in diseases such as rheumatoid arthritis, hay fever, contact dermatitis, insulin-dependent or type 1 diabetes, systemic lupus erythematosus, and graft rejection of transplanted solid organs, tissues, and cells. Each of these diseases has an underlying genetic component.

Genomic research supported by DAIT is yielding insights into the functional and structural dimensions of immune system regulation, hypersensitivity, and inflammation in diseases such as asthma, the dysregulation of immune responses that results in autoimmune disease, and basic mechanisms of immune tolerance and graft rejection. This research is important in the following areas:

- **Asthma and allergic diseases.** DAIT-supported research on the genetics of asthma, hypersensitivity, inflammation, and T cell mediation enables us to understand the mechanisms underlying these immune responses, resulting in improved diagnostic, prevention, and treatment strategies. Through genomic research, DAIT-supported investigators discovered that interleukin-4 (IL-4), a cytokine that is produced by helper T cells and mast cells, stimulates antibody production by B cells in a series of reactions involving several genes. Further studies on IL-4 might provide a marker for measuring asthma risk and severity.
- **Autoimmune diseases.** DAIT supports research on type 1 diabetes and other

autoimmune diseases that involve more than a single gene. Recent developments in genomics such as high-resolution DNA analysis and bioinformatics tools are making it possible to understand the underlying genetic causes of these complex diseases. For example, one approach compares the genes of individuals who have an autoimmune disease with those of healthy individuals to identify genetic and genomic differences that might be the underlying cause of disease. Between 10 and 20 distinct loci on the human genome may be responsible for susceptibility to type 1 diabetes. This knowledge will increase our ability to predict, diagnose, and treat this disease.

- **Transplantation.** DAIT-supported research on the genetics of graft rejection and immune tolerance is breaking new ground in the transplantation of solid organs, tissues, and cells for the prevention and treatment of disease. Genomic research funded by DAIT has identified surrogate markers of graft rejection in kidney transplant recipients. This research holds promise for the development of a noninvasive predictor of graft rejection based on gene expression analysis in urinary cells of transplant recipients.
- **Basic immunology research.** Basic research in immunology furthers our understanding of the properties, interactions, and functions of the cells of the immune system and the genetic aspects of immune system regulation and provides information about essential structural immunobiology. Recent breakthroughs in the basic science of immunogenetics inform clinical immunology, which may lead to the development of new immune-based therapies. Examples of basic immunology research supported by DAIT include the following:
 - Use of large-scale gene- and protein-expression analysis tools to describe pathways of cellular activation;

- Discovery of anti-inflammatory and immunosuppressive agents using DNA-based screening methods; and
- Analysis of genomic databases of T cell receptors and immunoglobulin gene sequences to link structural, functional, and clinical information.

Multicenter Research Programs

DAIT supports several multicenter research programs that include significant genomic efforts aimed at understanding the underlying mechanisms of immune-mediated diseases.

Immune Tolerance Network (ITN). The ITN is an international consortium of more than 80 investigators in the United States, Canada, Europe, and Australia dedicated to the clinical evaluation of novel, tolerance-inducing therapies in autoimmune diseases; asthma and allergic diseases; and rejection of transplanted organs, tissues, and cells. The goal of these therapies is to re-educate the immune system to eliminate harmful immune responses while preserving protective immunity against infectious agents. To understand the underlying mechanisms of action of the candidate therapies and to monitor tolerance, ITN has established state-of-the-art core laboratory facilities to conduct integrated mechanistic studies and to develop and evaluate markers and assays to measure the induction, maintenance, and loss of tolerance in humans. These core facilities include microarray analyses of gene expression, bioinformatics approaches to develop analytic tools for clinical and scientific data sets from the ITN-sponsored trials, enzyme-linked immunospot analyses of protein expression, and cellular assays for T cell reactivity. ITN has completed 2 clinical trials; 23 trials are ongoing or in development. ITN is co-sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases and the Juvenile Diabetes Research Foundation International. More information on the ITN is available at www.immunetolerance.org.

Autoimmunity Centers of Excellence (ACEs).

ACEs support collaborative basic and clinical research on autoimmune diseases, including single-site and multisite pilot clinical trials of promising immunomodulatory therapies. ACEs presently are enrolling participants in several clinical trials, including a trial of anti-CD20 in SLE and a trial of anti-C5 in lupus nephritis.

International Histocompatibility Working Group (IHWG).

IHWG is a network of more than 200 laboratories in more than 70 countries that applies new molecular techniques to population-based studies of histocompatibility genes. Histocompatibility genes allow the immune system to respond to specific pathogens, but these genes also play a role in the unwanted immune responses that occur in graft rejection and autoimmune diseases. Recent advances in genomics will facilitate the work of the human leukocyte antigen class II genes and related polymorphisms and their role in immunity, disease susceptibility, and graft rejection. Genomic techniques developed by IHWG investigators and others have shown a greater diversity among histocompatibility genes than was previously detected by conventional serologic methods. This work will bridge the gap between serologic and genomic definitions of these genes.

Multiple Autoimmune Disease Genetics

Consortium (MADGC). MADGC is a repository of genetic and clinical data and specimens from families in which two or more individuals are affected by two or more distinct autoimmune diseases. This resource provides materials to promote research aimed at discovering the human immune response genes

involved in autoimmunity. More information can be found at www.madgc.org.

North American Rheumatoid Arthritis

Consortium (NARAC). NARAC is a collaborative registry and repository of information on families with rheumatoid arthritis. The NARAC database contains information on 902 families, encompassing 1,522 patient visits. Of the 902 families, data for more than half have been validated, including 600 affected sibling pairs. The family registry and the repository samples should facilitate the characterization of the genes underlying susceptibility to rheumatoid arthritis and are available to all investigators. This registry is cosponsored by the National Institute of Arthritis and Musculoskeletal and Skin Diseases and the Arthritis Foundation. More information can be found at www.naracdata.org.

Primary Immunodeficiency Diseases Registry and Consortium.

In FY 2003, the Primary Immunodeficiency Diseases Consortium was established with support from NIAID and the National Institute of Child Health and Human Development. The Consortium (1) provides leadership and mentoring; facilitates collaborations; enhances coordination of research efforts; and solicits, reviews, recommends, and makes awards for pilot or small research projects; (2) maintains a primary immunodeficiency diseases registry, which provides data to the research community about the clinical characteristics and prevalence of these diseases; and (3) develops a repository of specimens from subjects with primary immunodeficiency diseases. Additional information on Consortium activities is available at www.usidnet.org.

The following is a list of NIAID-supported large-scale pathogen genome-sequencing projects active in fiscal year 2004:

ORGANISM	DISEASE
<i>Aedes aegypti</i>	invertebrate vector for yellow fever
<i>Anopheles gambiae</i>	malaria
<i>Aspergillus fumigatus</i>	aspergillosis
<i>Bacillus anthracis</i>	anthrax
<i>Bacillus cereus</i>	food poisoning
<i>Brugia malayi</i>	elephantiasis
<i>Burkholderia mallei</i>	glanders
<i>Burkholderia pseudomallei</i>	meliodosis
<i>Burkholderia thailandensis</i>	non-virulent strain
<i>Clostridium perfringens</i>	gas gangrene
<i>Coccidioides immitis</i>	respiratory infections; coccidioidomycosis
<i>Cryptococcus neoformans</i>	cryptococcosis
<i>Cryptosporidium parvum</i>	food-borne and water-borne diseases, gastritis
<i>Culex pipens</i>	invertebrate vector for West Nile virus
<i>Escherichia coli</i> K1 RS218	meningitis
<i>Ehrlichia</i> spp.	ehrlichiosis
<i>Entamoeba histolytica</i>	dysentery
<i>Francisella tularensis</i>	tularemia
<i>Giardia lamblia</i>	giardiasis
<i>Histoplasma capsulatum</i>	histoplasmosis
Influenza viruses	influenza
<i>Ixodes scapularis</i>	invertebrate vector for Lyme Disease
<i>Legionella pneumophila</i>	Legionnaire's disease
<i>Leishmania major</i>	cutaneous leishmaniasis
<i>Mycobacterium tuberculosis</i>	tuberculosis
<i>Mycobacterium smegmatis</i>	non-virulent strain
<i>Nematode species</i>	helminthiasis
<i>Plasmodium vivax</i>	malaria
<i>Pneumocystis carinii</i>	pneumonia, opportunistic disease
<i>Rickettsia rickettsii</i>	Rocky Mountain spotted fever
<i>Rickettsia typhi</i>	typhus
<i>Salmonella typhi</i>	typhoid fever
<i>Schistosoma mansoni</i>	dermatitis, Katayama fever, liver inflammation, fibrosis
<i>Streptococcus agalactiae</i>	Group B Streptococcus
<i>Streptococcus pneumoniae</i>	pneumonia, meningitis
<i>Toxoplasma gondii</i>	toxoplasmosis, congenital, and ocular infections, opportunistic disease
<i>Trichomonas vaginalis</i>	vaginitis
<i>Trypanosoma brucei</i>	trypanosomiasis
<i>Trypanosoma cruzi</i>	Chagas disease
<i>Vibrio cholerae</i>	cholera
<i>Wolbachia</i>	endosymbiont of filarial nematodes and insect vectors
<i>Yersinia pestis</i>	plague

GLOBAL HEALTH

The NIAID research mission in infectious and allergic diseases is of global importance. When combined, these conditions are the most common causes of preventable human illness and death around the world. Recent concern about emerging and re-emerging infectious diseases and the anthrax biological weapon attacks of October 2001 further reinforced the importance of and added new dimensions to NIAID-supported research in improving early diagnosis, prevention, and control of these pathogens.

Formal recognition of the importance of international research dates back to the International Health Research Act (1960), which gave the Secretary of Health, Education, and Welfare—now the Secretary of Health and Human Services—the authority to conduct research activities outside the United States, provided that the activities were beneficial to the health of U.S. citizens. This authority has been delegated to the NIH and to NIAID. The Public Health Service Act of 1988 (Public Law 100–607) created new HIV/AIDS authorities for the NIH. Subsequently, the NIH Revitalization Act (1993) gave NIAID specific authority to conduct research on tropical diseases that disproportionately affect populations in resource-poor and economically restructuring countries.

In May 2001, NIAID announced its Global Health Research Plan for HIV/AIDS, Malaria, and Tuberculosis. The Global Plan provides short-, medium-, and long-term objectives for treating, preventing, and controlling these diseases by building on the Institute's strong foundation in infectious disease research.

Intramural Research Training and Collaborative Research

NIAID laboratories located in the Bethesda/Washington metropolitan area and Hamilton, Montana, are a significant source of research training for postdoctoral non-U.S. scientists.



Public reaction in India to international effort to reduce cholera outbreaks.

NIAID is also responsible for the management of the Dale and Betty Bumpers Vaccine Research Center (VRC). The host NIAID laboratory usually provides the stipend for the visiting scientists. The research training experience often results in long-term intramural international collaborations once the scientists return to their home countries. In fiscal year (FY) 2004, the largest numbers of NIAID international scientists were from China, India, Japan, France, Canada, Germany, and Italy.

Several years ago, the NIAID Division of Intramural Research (DIR) initiated the International Centers for Excellence in Research (ICER) program to develop sustained research activities in areas of high infectious disease burden through partnerships with scientists in developing countries. The ICER program builds on the long-standing collaboration in malaria research with scientists in Mali, West Africa. While DIR provides the core research program at each ICER site, it is anticipated that other NIAID programs and NIH Institutes and Centers will provide opportunities to expand the research capabilities and programs through the extramural community. Although focused on clinical research in infectious disease, each ICER has the capability to address a range of research and training activities. Current ICER sites are in India, Mali, and Uganda.

The VRC, in collaboration with the Makerere University–Walter Reed Project and the NIAID Division of AIDS, will expand ongoing phase I clinical trials in the United States of a novel HIV-1 DNA vaccine directed at the three most globally important HIV-1 subtypes (clades) to Uganda in the coming year.

Domestic Research Awards with an International Component

NIAID funds the vast majority of its international research indirectly through competitive domestic extramural research awards that have an international component. Special emphasis programs have been developed in tropical medicine, emerging infectious diseases, HIV/AIDS, and tuberculosis to take advantage of research opportunities overseas in countries with a disproportionate burden of these diseases.

The infectious disease clinical research efforts supported by NIAID include international sites. Initiated in 1994, the NIAID Tuberculosis Research Unit is supported by a research contract with Case Western Reserve University and funds an international cross-disciplinary team of investigators in Brazil, the Philippines, South Africa, Uganda, and the United States to conduct high-priority research. This research addresses complex clinical questions about tuberculosis and provides the scientific framework upon which high-quality clinical trials of new vaccines, therapeutics, and diagnostics can be conducted. The STD Clinical Trials Units also support sites in Madagascar and Uganda. In addition, the NIAID Bacteriology and Mycology Study Group has begun clinical trials in Thailand. Clinical site development continues in Ghana and Mali for malaria vaccine trials.

NIAID also supports a number of research programs that focus on tropical infectious diseases. The International Collaboration in Infectious Disease Research (ICIDR) Program, initiated in 1980, makes awards to U.S. institutions to engage in substantial international

collaboration with overseas institutions in tropical medicine and emerging infectious diseases. The ICIDR Program will be re-competed in FY 2005.

In the context of conducting international research, NIAID supports the development of independent research capacity at NIAID-funded institutions. Numerous training activities have been conducted in Africa, India, South America, and Southeast Asia. This training includes good clinical practices, international research ethics, institutional review board administration, scientific writing, and the design and conduct of clinical trials.

DAIDS research networks have both domestic and international components. The HIV Vaccine Trials Network (HVTN) is a comprehensive, clinically based global network with a mission to develop and evaluate preventive HIV vaccines. The HVTN includes international sites located in Africa (Botswana, Malawi, and South Africa), Asia (China, India, and Thailand), the Caribbean (Dominican Republic, Haiti, Jamaica, Puerto Rico, and Trinidad and Tobago), and South America (Brazil and Peru).

The HIV Prevention Trials Network (HPTN) is a second worldwide collaborative effort established by NIAID to evaluate the safety and efficacy of nonvaccine prevention interventions. The HPTN consists of domestic and international units. International sites are located in Brazil, China, India, Malawi, Peru, Russia, South Africa, Tanzania, Thailand, Uganda, Zambia, and Zimbabwe.

NIAID's Acute HIV Infection and Early Disease Research Program is collaborating with the University of Alabama at Birmingham and the University Teaching Hospital in Lusaka, Zambia, to study the effects of a short course of antiretroviral therapy on the viral load in newly infected persons when it is initiated early after acute HIV infection.

The NIAID Centers for AIDS Research (CFARs) support a multidisciplinary environment that promotes basic, clinical, behavioral, and translational research in the prevention, detection, and treatment of HIV infection and AIDS. Current CFAR collaborations are taking place in Belize, Kenya, Mexico, Peru, Thailand, Uganda, and Zambia.

International Awards

NIAID and the NIH accept investigator-initiated research proposals from international scientists and permit international scientists to respond to most program announcements and requests for applications. To be funded, international applications must receive a competitive peer review score and be approved by the National Advisory Allergy and Infectious Diseases Council on the basis of their uniqueness and/or program relevance. International scientists also may be eligible to compete for NIAID research contracts when U.S. institutions cannot carry out the project (e.g., pertussis vaccine trials in Italy and Sweden) or when the domestic applications are not responsive to the solicitation.

Historically, international awards have accounted for about 1 percent of the NIAID budget. As basic research results in new or improved products that require evaluation in populations with heavy burdens of disease, this amount is expected to increase. Furthermore, long-term NIAID investment in collaborative research has resulted in the development of overseas sites capable of independent research. The establishment of the Tropical Medicine Research Centers (TMRC) program a decade ago was a reflection of this phenomenon. Currently, TMRCs are located in Brazil, Chile, Colombia, and Peru.

In FY 2001, NIAID launched the Comprehensive International Program of Research on AIDS (CIPRA). CIPRA provides long-term support directly to developing countries to plan and implement a comprehensive HIV/AIDS prevention and research agenda

relevant to their populations and to strengthen the infrastructure required to carry out this research. In FY 2004, CIPRA awarded five new CIPRA grants to the following countries: Cambodia, Haiti, Peru, Russia, and Thailand. In addition, there are ongoing CIPRA projects in Argentina, Brazil, China, Egypt, the Republic of Georgia, Kenya, Mozambique, Senegal, and South Africa.

In FY 2003, NIAID initiated the International Research in Infectious Diseases (IRID) Program, which consists of small grants programs specifically designed to help foreign scientists in resource-constrained countries obtain NIH funding. To date, IRID awards have been made to investigators in Africa, Eastern Europe, South America, and the South Pacific.

Official Bilateral Programs

In addition to regular scientific channels, the United States often develops formal, bilateral scientific agreements with foreign governments or organizations at the level of the President, the Department of Health and Human Services (DHHS), the NIH, or NIAID. NIAID carries out these programs with budgeted funds unless special or supplementary funds are made available. NIAID has actively participated in bilateral programs involving Brazil, China, France, the Republic of Georgia, Germany, India, Italy, Japan, Russia, South Africa, and Taiwan. Of particular interest is the U.S.–Japan Cooperative Medical Science Program (USJCMSP), which consists of committees of senior scientists and panels of experts in high-priority diseases of the Pacific Basin. Both the Joint USJCMSP Committee and Joint Panels meet annually, alternating countries in conjunction with scientific conferences. The USJCMSP has organized annual workshops on emerging and re-emerging infectious diseases in the Pacific Basin at different sites in the region. Active priority areas are AIDS, acute respiratory infections, cholera and other bacterial enteric diseases, environmental genomics and carcinogenesis, infectious hepatitis, immunology,

leprosy/tuberculosis, nutrition and metabolism, parasitic diseases, and viral diseases.

International Agencies and Organizations

NIAID has joined with other organizations to enhance scientific collaborations in combating infectious diseases. Examples include the Presidential Millennium Vaccine Initiative; the Global Alliance for Vaccines and Immunization; the Multilateral Initiative on Malaria in Africa; the International Cooperative Biodiversity Groups Program; and the DHHS–State Department Biotechnology Engagement Program and the Civilian Research and Development Foundation, both of which provide support to scientists in newly independent states of the former Soviet Union to conduct collaborative research on problems of public health importance.

NIAID staff members also participate on the scientific boards of and as consultants to the World Health Organization, the Pan American Health Organization, and the U.S. Agency for International Development.

On February 23, 2004, the first \$350 million in funding of the President’s Emergency Program for AIDS Relief (PEPFAR) was made available and began reaching people in need only 2 weeks later. The second distribution of funding—\$500 million—will continue to build on prevention, treatment, and care efforts. In total, PEPFAR will spend \$2.4 billion on global AIDS through FY 2005. PEPFAR countries include Botswana, Cote d’Ivoire, Ethiopia, Guyana, Haiti, Kenya, Mozambique, Namibia, Nigeria, Rwanda, South Africa, Tanzania, Uganda, Vietnam, and Zambia. NIAID currently supports the work of PEPFAR in Ethiopia, Haiti, and South Africa.

HEPATITIS C

Before 1990, patients who received blood transfusions were vulnerable to an unknown infectious agent of liver disease then known only as non-A, non-B hepatitis. However, after being cloned and genetically sequenced more than a decade ago, the hepatitis C virus (HCV) was identified as the cause of most of these unidentified, transfusion-related liver infections.

Hepatitis C continues to emerge as a serious infectious disease in the United States and worldwide. Chronic hepatitis C infection can lead to liver inflammation, cirrhosis, and cancer. HCV infects more than 170 million people worldwide, including 3.9 million people in the United States.³⁵ About 25,000 new U.S. infections occur each year,³⁶ and liver failure resulting from HCV infection is the leading cause of liver transplants in the United States.

Fortunately, rapid improvements in HCV diagnostics, including tests that can detect both antibodies to the virus and the virus itself, have made the supply of blood and blood products in this country safe from HCV contamination. Today, injection drug users are at highest risk of infection. Sexual transmission also occurs, especially among people with multiple partners; other transmission routes are also possible, including exposure to contaminated blood. Approximately 55 to 85 percent of infected people become chronic carriers of the virus.³⁷ However, because people with chronic HCV infection often show no overt symptoms even as their livers are being attacked by the virus, many current carriers do not know they are infected.

NIAID has aggressively expanded its HCV research program through its Framework for Progress on Hepatitis C. In collaboration with participating Institutes and Centers, NIAID developed an NIH-wide framework that incorporates the different missions of NIH into a cohesive global plan for hepatitis C research. The final plan was reviewed by outside experts

and has been approved by NIH Institute and Center Directors and the NIH Director. The plan identified the following research goals:

- Understand transmission modes to develop effective intervention strategies.
- Understand pathogenic mechanisms and disease progression to develop new treatment.
- Characterize host immune responses to infection in order to develop new vaccines and therapies.
- Define viral replication and recovery during therapy.
- Investigate clinical manifestations in order to develop methods to noninvasively evaluate disease state, predict outcomes, and prevent or reverse disease progression.
- Define effective prevention and intervention strategies to improve health.

The tools needed to achieve these goals include tissue culture systems, small-animal models, well-defined clinical cohorts, and research and reference reagents and tools.

Current hepatitis C therapies include various forms of interferon, an interferon-ribavirin combination, and long-lasting forms of interferon with and without ribavirin. Each new therapy has resulted in improved response rates. However, these drugs have a significantly lower success rate in African Americans and in patients infected with the viral strain—called genotype 1—that predominates in the United States; a total of six distinct genotypes have been identified. Studies suggest that African Americans infected with genotype 1 and treated with interferon for HCV have a lower end-of-treatment response than do Whites. NIAID funds both basic research on HCV and product development for viral therapeutic targets, including inhibitors of viral components such as the polymerase, protease,

helicase, and internal ribosome entry site, as well as other viral components critical for replication.

Extramural investigators developed HCV cell lines that are now validated as *in vitro* antiviral screening tools. NIAID supports two of these systems via its *in vitro* screening contract programs; they can be accessed through this program by both academic and corporate scientists. Further information is available at www.niaid.nih.gov/dmid/viral.

A major reason that many people cannot clear HCV infection is that the virus subverts the immune response through a process called immune evasion. Thus, defining and overriding these evasion strategies through rational design of vaccines and immunotherapies is an important area of emphasis for NIAID-supported HCV research and development.

NIAID intramural and extramural investigators also are conducting many research activities that will help pave the way for the development of HCV vaccines. Recent efforts to develop HCV vaccines have been related primarily to the identification of immune responses—both protective and evasive—in infected humans and experimentally-infected chimpanzees. NIAID recently launched a phase I trial of Chiron Corporation's prototype E1E2 HCV vaccine, intended to evaluate the safety, tolerability, and immunogenicity of this vaccine candidate in healthy, uninfected human subjects.

The extramural program of NIAID has initiated two activities to further enhance its research and development activities. The first activity is the acquisition and provision of HCV research reagents, which are now provided through the AIDS Research and Reference Reagent Program (www.aidsreagent.org). Other HCV-related reagents are available through the NIH Tetramer Facility (www.niaid.nih.gov/repos/tetramer/index.html) and the NIAID Reference Reagent Repository (www.bratonbiotech.com/braton11.htm). The second activity is the development of

an annotated HCV sequence database by Los Alamos National Laboratories (<http://hcv.lanl.gov/content/hcv-db/index>).

In 2002, NIAID cosponsored the “Management of Hepatitis C: 2002” Consensus Development Conference. The meeting was convened to provide an update to a 1997 conference on the same topic. Among the recommendations for future research in its report,³⁸ the panel gave top priority to the development of reliable and reproducible HCV cultures, which will advance the understanding of HCV biology and mechanisms of drug resistance and aid vaccine development. The panel also urged the establishment of a hepatitis research network that would conduct research into the natural history, prevention, and treatment of hepatitis C.

NIAID supports a robust hepatitis C research portfolio that encompasses many of these areas. In particular, NIAID supports the Hepatitis C Cooperative Research Centers Network, which unites basic and clinical researchers investigating hepatitis C infection and disease to identify new and better means of prevention and treatment. Through this network, NIAID supports clinical research that emphasizes studies in special populations heavily affected by HCV such as African Americans, who tend to respond poorly to standard therapies. NIAID also continues to help support the ancillary studies of the Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) trial of the National Institute of Diabetes and Digestive and Kidney Diseases. This trial is evaluating the impact of long-term therapy on disease progression, including virologic and immunologic responses and their association with recovery.

Scientists in NIAID's Division of Intramural Research are conducting research to answer key questions about HCV pathogenesis and the host immune response in order to develop an effective HCV vaccine and better hepatitis C treatments. Along the way, they are improving the tools used in hepatitis research. They are also developing

critical research reagents and sharing them with researchers around the country.

For example, NIAID scientists collaborated with colleagues in France to demonstrate that a new *in vitro* test to detect and quantify virus neutralizing antibodies worked as well as a more cumbersome test that requires the use of chimpanzees.³⁹ This finding will help researchers identify the specific portions of HCV that induce protective antibodies and promote the development of an effective hepatitis C vaccine.

The scientists then used the new assay to test batches of commercial immune globulin manufactured before and after the initiation of HCV screening of the donated blood plasma used to make it. They found that batches manufactured before HCV screening contained high levels of neutralizing antibody and were not associated with HCV infections in recipients. In contrast, immune globulins manufactured after initiation of screening for HCV lacked neutralizing antibodies and were associated with many cases of hepatitis C in recipients. This work conclusively

demonstrates that neutralizing antibodies protect humans from HCV infection and provides for the first time a rational basis for passive antibody-based prevention of hepatitis C.

Basic research, as well as vaccine and therapeutic development, would be greatly aided by the development of a small-animal model in which to study HCV and to fine-tune candidate vaccine formulations. To this end, NIAID researchers are working to determine whether the GB virus B (GBV-B), a monkey virus that is the closest relative of HCV, is a suitable surrogate for HCV in experimental studies. If so, then the tamarin monkey could be used for *in vivo* studies and greatly reduce the need for chimpanzees for HCV research. Work in this area has been encouraging. For example, NIAID scientists recently reported that the p7 protein of HCV is critical for infectivity and represents a new target for HCV drug development.⁴⁰ They have since gone on to show that a p7-like protein of GBV-B exists and is also essential for infectivity, strengthening the relevance of GBV-B as a model of HCV.

IMMUNE TOLERANCE

The immune system is precisely tuned to distinguish biochemical structures that belong to the body from those that do not, allowing it to swiftly deploy a potent array of defense mechanisms whenever evidence of a foreign invasion is found. But many diseases, including autoimmune disorders, allergic diseases, and transplant rejection, are themselves caused by inappropriate immune system responses. To fight these disorders, researchers are now building on two decades of intensive basic research in immunology to develop treatments that can induce the immune system to tolerate specific antigens. Recent progress in the development of these therapies, which have the potential to be both very potent and broadly applicable, has been very encouraging.

All tolerance-induction strategies share a common goal: to selectively prevent or diminish specific harmful immune responses without disabling the immune system as a whole. In autoimmune diseases, the idea is to make the immune system tolerant to the specific, normally occurring antigens that cause it to attack the body's own organs, tissues, or cells. In asthma and allergic diseases, the goal is to prevent responses to allergens such as cockroach and house dust mite that cause or exacerbate these diseases. For transplant rejection, the goal is to selectively block immune responses directed against the foreign antigens on the graft, and thereby allow long-term graft survival without the heightened risks of infection, malignancy, and atherosclerosis associated with current immunosuppressive therapies.

NIAID supports a wide range of programs to turn the promise of immune tolerance therapies into reality. Many of these are carried out by NIAID's Division of Allergy, Immunology, and Transplantation (DAIT), which supports basic research into the mechanisms responsible for immune tolerance, translational research to facilitate the application of immune-tolerance

approaches to human diseases, and clinical research to evaluate new therapies that can induce and maintain immune tolerance. New approaches are being investigated to:

- Improve understanding of the molecular mechanisms responsible for the induction and maintenance of immune tolerance;
- Replace or improve suboptimal treatment protocols for immune-mediated diseases;
- Discover methods to prevent or reverse immune-mediated disorders for which no effective therapies are currently available;
- Create an efficient research infrastructure for the development and rapid testing of tolerogenic agents in human immune-mediated diseases; and
- Clarify mechanisms by which tolerogenic agents suppress disease.

NIAID, along with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the Juvenile Diabetes Research Foundation International, cosponsors the Immune Tolerance Network (ITN), an international consortium of more than 80 investigators in the United States, Canada, Europe, and Australia dedicated to the clinical evaluation of novel, tolerance-inducing therapies for autoimmune diseases, asthma and allergic diseases, and transplant rejection. ITN conducts integrated studies on the mechanisms that underlie immune tolerance and develops markers and assays to measure the induction, maintenance, and loss of tolerance in humans. The network has established several state-of-the-art core facilities and has supported 18 approved clinical protocols, as well as several additional studies of the immune mechanisms involved in tolerance. ITN is currently involved in the following areas of clinical research:

- Allergy
- Asthma
- Diabetes
- Islet cell, kidney, and liver transplantation
- Bone marrow transplantation
- Multiple sclerosis (MS)
- Psoriatic arthritis
- Systemic lupus erythematosus

Examples of active ITN clinical research studies include:

- A phase II placebo-controlled trial to evaluate the safety and efficacy of a treatment for ragweed allergy that involves a combination of omalizumab—an anti-IgE antibody—and immunotherapy. A followup study will examine whether persistent immunologic and clinical tolerance has been achieved.
- A phase I trial to analyze and monitor the safety of immunization with a fragment of the human insulin B chain in subjects newly diagnosed with type 1 diabetes; the hope is that this “autoimmunization” therapy will increase immune tolerance of insulin-producing cells.
- A pilot study to evaluate the safety and efficacy of a treatment regimen to induce tolerance in kidney transplant recipients. In this study, patients will receive low-dose steroid-free immunosuppression, two donor stem cell infusions, and an antibody called Campath-1H, which selectively eliminates immune system T cells involved in organ rejection. Treatment will be withdrawn after 1 year and the patients followed to see if long-term tolerance has been achieved.
- A phase I study in 16 patients with relapsing-remitting MS to assess the safety of one dose

of CTLA4-IgG4m, an antibody that may block a pathway that allows the immune system to attack nervous system tissue.

- A phase II multicenter trial to evaluate the lipid-lowering drug atorvastatin in patients at high risk of developing MS.

Tolerance assays—tests and procedures to monitor patient responses to tolerance therapies—are critically needed to better evaluate tolerance-inducing therapies during and after clinical trials. ITN has therefore established a set of core laboratories to develop assays for the induction, maintenance, or loss of immune tolerance. These core facilities carry out microarray analyses of gene expression, develop analytic tools for clinical and scientific datasets from ITN-sponsored trials, and conduct enzyme-linked immunospot (ELISPOT) assay analyses of protein expression and cellular assays for T cell reactivity.

Examples of current ITN efforts to develop mechanistic assays include:

- Development of antigen-specific assays for donor-specific tolerance in renal transplant recipients;
- Cytokine production in children with preclinical and clinical type 1 diabetes; and
- Identification and mechanistic investigations of tolerant kidney transplant patients.

More information on ITN’s mission and research is available at www.immunetolerance.org.

In collaboration with NIDDK, DAIT supports the Nonhuman Primate Transplant Tolerance Cooperative Study Group (NHPCSG). The goal of this program is to evaluate the safety and efficacy of novel tolerogenic regimens in preclinical models of kidney and islet transplantation. Scientists in this study group have demonstrated long-term graft acceptance using tolerogenic regimens in both kidney and

islet allograft recipients. In FY 2002, this program was expanded from 3 to 10 research grants. This expansion has allowed a larger number of tolerance-induction strategies to be rigorously evaluated, allowed the sharing of valuable resources, and facilitated the development of new collaborations. In FY 2005, the NHPCSG will be further expanded to include heart and lung transplantation. To accelerate research conducted through this program, DAIT maintains breeding

colonies of specific pathogen-free rhesus and cynomolgus macaques.

Other DAIT-supported research programs that include studies on immune tolerance are the Autoimmunity Centers of Excellence, Innovative Grants on Immune Tolerance, and program projects in basic biology, basic immunology, and transplantation tolerance.

MALARIA

Malaria, a serious disease caused by parasites of the genus *Plasmodium* and transmitted by mosquitoes, continues to pose a tremendous public health burden for people living in the tropics, particularly in Africa. Globally, malaria causes more than 1 million deaths each year and continues to be the most important tropical parasitic disease in terms of annual mortality. Approximately 60 percent of malaria deaths occur in the poorest 20 percent of the total global population, with the majority of deaths occurring in children aged 5 years and younger in sub-Saharan Africa.⁴¹ Unfortunately, malaria parasites have developed a variety of mechanisms to evade host immune responses, thus making the development of a successful vaccine very challenging.

Malaria research at the NIH dates back to the 1930s, when malaria was still a major public health problem in the United States. NIAID is currently one of the world's leading supporters of malaria research. NIAID maintains a broad malaria research portfolio that includes parasite biology, pathogenesis, drug development, vaccine development, epidemiology, and vector control. NIAID-funded malaria research is conducted by scientists at institutions throughout the United States, including NIAID's own intramural laboratories, and overseas.

NIAID's intramural malaria vaccine research program is centered in the Malaria Vaccine Development Branch (MVDB). The MVDB collaborates with a number of investigators within the United States and throughout the world, as well as with the extramural NIH malaria program and a variety of funding organizations such as the U.S. Agency for International Development and the Malaria Vaccine Initiative supported by the Program for Appropriate Technology in Health (PATH). The MVDB has produced multiple vaccine components using the quality control practices required for manufacturing clinical materials. Two of these have been

combined into a vaccine called AMA1-C1, which was well tolerated in a phase I trial in U.S. adults and further tested in a phase I study in adults in Mali, marking the first time that MVDB products have been tested in a malaria endemic area. MVDB researchers are working to improve the immunogenicity of this formulation, in collaboration with Coley Pharmaceutical Group, Inc., and to broaden the reactivity of anti-AMA1 antibody response. In addition, they have completed the preclinical studies for two other vaccine candidates and have initiated a phase I clinical trial in U.S. adults as a prelude to anticipated future studies in an endemic area in Africa. Thus, the past year has seen a significant expansion of phase I clinical trials for multiple malaria vaccine candidates. The lack of significant adverse reactions to these vaccine formulations provides the basis for moving to additional studies in malaria-endemic areas in order to answer critical questions about the safety and efficacy of these vaccines in African children.

Intramural investigators also are conducting basic studies aimed at providing fundamental biological information for the development of diagnostics, therapeutics, and other control measures against the disease. For example, Division of Intramural Research scientists are using the malaria parasite genome databases and microarray analysis to identify genes that may be involved in drug resistance and parasite sexual development. Identifying these genes is an important step in developing measures to interrupt parasite transmission and will provide critical information for drug and vaccine development. In addition, to understand the factors that determine the severity of malaria, NIAID investigators are studying how hemoglobin C and hemoglobin S (sickle-cell hemoglobin) protect children from severe and fatal complications of malaria caused by *Plasmodium falciparum*.

Through its extramural malaria research program, NIAID also supports extensive research on malaria vaccines conducted by researchers from academia and industry. The Institute currently

funds multiple studies aimed at developing vaccines against different stages of the malaria parasite and has conducted clinical trials in the U.S. and abroad of the most promising candidates. These research efforts represent a critical component of NIAID's Research Plan for Malaria Vaccine Development, which is designed to accelerate research leading to the development of malaria vaccines. Under a contract with Science Applications International Corporation, NIAID established a capability to undertake targeted research essential to translating basic research concepts into prototype vaccine products for clinical evaluation. Recent activities included process development for production of novel candidate vaccines, production and qualification of critical reagents for quality control of new candidate vaccines, and preclinical safety evaluation of promising candidate vaccines prior to entry into clinical trials. Reagents were also provided to the Malaria Research and Reference Reagent Resource, which will make them available to the international malaria research community.

NIAID has undertaken a phase I trial of a novel candidate malaria vaccine at the University of Maryland Center for Vaccine Development. This vaccine was developed with grant support from the Small Business Innovation Research Program administered at NIAID, and with additional support and collaboration from the Malaria Vaccine Initiative at PATH. Results of this trial are expected to be available for analysis in mid-2005. Additional clinical trials of promising vaccine candidates are planned through the Vaccine and Treatment Evaluation Units.

A key component of the NIAID Research Plan to Accelerate Malaria Vaccine Development has been the establishment of research centers in malaria-endemic areas that can support epidemiological and clinical research relevant to malaria, as well as conduct clinical trials. In June 2003, in collaboration with the Walter Reed Army Institute of Research, the University of Maryland Center for Vaccine Development, and

the University of Bamako (in Mali), NIAID launched its first trial of a novel candidate malaria vaccine in Mali. A full analysis of this phase I trial will be completed in 2004. A second clinical trial with a different candidate vaccine was begun in Mali in late 2004.

Identification, validation, and evaluation of new antimalarial therapies remain NIAID priority activities. In 2004, NIAID issued a renewal of the Tropical Diseases Research Units (TDRU) program. The objective of the TDRU program is to support translational research leading to the discovery and preclinical development of new drugs or vector control methods to reduce or eliminate morbidity and mortality resulting from parasitic infection. One of the three new awards made under this program will focus on development of novel antimalarials. Requests for applications for collaborations with private companies for the development of new compounds and strategies for malaria treatment and mosquito control have been funded by the Challenge Grants and Partnerships program. These initiatives are currently supporting studies aimed at the clinical development of two new antimalarial compounds in collaboration with large pharmaceutical companies, screening and candidate validation of novel classes of compounds, exploring the use of larval control strategies for certain areas of malaria transmission in Africa, mitigating insecticide resistance, and developing new environmentally safe insecticides targeting mosquito activities. NIAID also supported a phase I clinical trial of a chloroquine-analog effective against chloroquine-resistant *P. falciparum*, as well as investigator-initiated research on preclinical development and evaluation of novel compounds. The Institute is also supporting preclinical and clinical studies of combination therapies for malaria, especially those including artesunate.

Clinical research capacity continues to be strengthened in overseas sites in Ghana and Mali in West Africa with support by contracts under the "Malaria: Clinical Research and Trial

Preparation Sites in Endemic Areas” initiative. Research staff members have and continue to participate in training in epidemiology, bioethics, good clinical practice, good laboratory practice, and financial management. Clinical facilities, research and clinical safety laboratories, and satellite Internet connectivity have been established or expanded.

NIAID also continues to participate in the Federal Malaria Vaccine Coordinating Committee, and provides support to the Multilateral Initiative on Malaria and the World Health Organization (WHO) Special Programme for Research and Training in Tropical Diseases Task Force to advance malaria research and research capacity strengthening activities at African institutions. NIAID also participates in the Malaria Vaccine Advisory Committee established at the WHO Initiative for Vaccine Research, and in the External Scientific Advisory

Committee of the Medicines for Malaria Venture, a public-private partnership that fosters the accelerated development of new antimalarial compounds. NIAID has also worked with the European Commission and the European-Developing Countries Clinical Trial Partnership to coordinate product development and clinical trial activities in vaccines and drugs.

In addition to the targeted activities listed above, malaria-related research and training activities are supported under a number of other programs, such as the TRDUs, International Centers for Tropical Diseases Research Network, U.S.–Japan Cooperative Medical Science Program, Indo–U.S. Vaccine Action Program, and Clinical Research and Training Opportunities. Additional information is available at the following Web site: <http://www.niaid.nih.gov/ictdr/tdru.htm>.

MINORITY AND WOMEN'S HEALTH

NIAID's Office of Special Populations and Research Training (OSPRT) provides oversight and coordination to the Institute's activities in the area of minority and women's health. OSPRT has provided the National Center for Minority Health and Health Disparities with benchmarks on progress made to initiatives contained in the NIAID fiscal year (FY) 2002–2006 *Strategic Plan for Addressing Health Disparities*. The plan lists three goals: (1) to conduct research to identify and address health disparities among various populations affected by infectious and immunologic diseases; (2) to increase the number of minority scientists and grantees; and (3) to improve education and outreach activities for the transfer of health information to these populations. NIAID continues to prioritize basic, clinical, and epidemiologic research on the health problems of minorities and women; efforts to increase participation of minority scientists in its research programs; and outreach activities designed to communicate research developments to these populations. (For the NIAID *Strategic Plan for Addressing Health Disparities*, see: www.niaid.nih.gov/healthdisparities/niaid_bd_plan_final.pdf.)

OSPRT staff played a major role in updating the NIH report, *Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research*, as required by the Government Accountability Office. OSPRT staff also assisted in the development of the *Outreach Notebook* for extramural principal investigators who conduct or plan to conduct clinical trials with human subjects. (For the NIH report, *Monitoring Adherence to the NIH Policy on the Inclusion of Women and Minorities as Subjects in Clinical Research*, see: www4.od.nih.gov/orwh/Updated_2002-2003.pdf; for the *Outreach Notebook*, see: www4.od.nih.gov/orwh/outreach.pdf.)

Minority and Women's Health Programs

Many infectious, immunologic, and allergic diseases affect minorities and women at disproportionately high rates and fall under the mandate of NIAID. The Institute conducts research, either through its own laboratories or through funded mechanisms, on a broad spectrum of these diseases. Additionally, the Institute collaborates with other organizations to address health disparities in these populations.

Asthma. Asthma is a chronic disease affecting more than 18 million Americans. It disproportionately affects minorities, particularly African American and Hispanic children residing in inner cities. Results from the Inner-City Asthma Study, cosponsored by the National Institute of Environmental Health Studies, indicate that physician education and an extensive environmental intervention successfully reduced allergen levels in the homes of inner-city children with asthma. This reduction resulted in an improvement in asthma morbidity, measured by decreases in asthma symptoms, number of hospitalizations, and number of unscheduled physician visits for asthma. The reduction continued 1 year post-intervention. The physician feedback intervention resulted in a 20 percent decrease in unscheduled emergency room or clinic visits for poorly controlled asthma.⁴² These findings should lead to significantly improved health for inner-city children with asthma and reduce the high medical, economic, and social costs associated with this disease.

Autoimmune diseases. Autoimmune diseases are those in which the immune system mistakenly attacks the body's own cells, tissues, and organs. Autoimmune diseases affect an estimated 5 to 8 percent of the U.S. population, approximately 14 to 22 million people. Several of these diseases disproportionately affect women and minority populations. For example, in some autoimmune diseases, including thyroiditis, scleroderma, systemic lupus erythematosus

(SLE), and Sjögren's syndrome, females represent 85 percent or more of patients. Ninety percent of the nearly 2 million Americans diagnosed with (or suspected of having) SLE are women. SLE damages multiple tissues and organs and may affect muscles, skin, joints, and kidneys, as well as the brain and nerves. In other diseases such as multiple sclerosis, myasthenia gravis, and inflammatory bowel diseases, the disparity is smaller, with females representing 55 to 70 percent of patients. The reasons for these gender-based variations are not known.

NIAID supports a broad range of basic and clinical research programs in autoimmunity, including the Autoimmunity Centers of Excellence, the Autoimmune Diseases Prevention Centers, and multidisciplinary research on gender-based differences in immune responses. Through the Stem Cell Transplantation for Autoimmune Diseases Consortium, NIAID is developing clinical trials to assess the efficacy of hematopoietic stem cell transplantation to treat severe multiple sclerosis, SLE, and scleroderma. The consortium will conduct studies of the underlying immune mechanisms of these diseases as well. NIAID chairs the trans-NIH Autoimmune Diseases Coordinating Committee (ADCC), which submitted its Research Plan to Congress in December 2002. The ADCC expects to submit its third report to Congress in early 2005, which will include NIH accomplishments and activities in autoimmune diseases research. (For the ADCC Research Plan, see: http://www.niaid.nih.gov/dait/pdf/ADCC_Report.pdf.)

Collaborations among NIAID, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and the Juvenile Diabetes Research Foundation International established the Immune Tolerance Network (ITN), an international consortium dedicated to the clinical evaluation of novel, tolerogenic approaches for the treatment of autoimmune diseases, asthma and allergic diseases, and the prevention of graft rejection. ITN also conducts integrated studies on the underlying mechanisms of these approaches and

develops and evaluates markers and assays to measure the induction, maintenance, and loss of tolerance in humans. ITN includes more than 80 basic and clinical scientists and physicians at more than 40 institutions in the United States, Canada, Europe, and Australia. (For more information about the ITN, see: www.immunetolerance.org.)

Hepatitis C. Hepatitis C virus (HCV) infection is the most common chronic bloodborne viral infection in the United States. HCV disproportionately affects minority populations, particularly African Americans and Hispanics. Moreover, available treatments for HCV tend to be less effective for African Americans than for other populations.⁴³

To investigate this issue, NIAID is supporting a study to determine whether there are specific genetic and molecular factors that cause African American patients to respond poorly to the standard interferon and ribavirin therapy used for hepatitis C that seems to be effective in White populations. Understanding the reasons for differential drug responses among these populations may lead to the development of new HCV-targeted drugs. In particular, NIAID supports the Hepatitis C Cooperative Research Centers Network, which unites basic and clinical researchers investigating HCV infection and the disease process to identify new and better means of prevention and treatment.

HIV/AIDS. HIV/AIDS continues to disproportionately affect minorities. Racial and ethnic populations in the United States, primarily African Americans and Hispanics, constitute 58 percent of the more than 880,000 cases of AIDS reported to the Centers for Disease Control and Prevention (CDC) since the epidemic began in 1981. African Americans make up almost 40 percent of all AIDS cases reported in the United States, yet according to the U.S. Census Bureau, they comprise only 13 percent of the U.S. population. Hispanics represent 18 percent of all AIDS cases and are approximately 14 percent of the U.S. population. Of the new AIDS cases

reported in 2003, 49 percent were among African Americans, 20 percent among Hispanics, 28.3 percent among Whites, and 1.7 percent among American Indians/Alaska Natives and Asian Americans/Pacific Islanders. Among women, African Americans and Hispanics account for 83 percent of AIDS cases; among men, African Americans and Hispanics account for 64 percent of cases. Injection drug use is a major factor in the spread of HIV in minority communities. Other factors contributing to the spread of HIV/AIDS in these communities include men who have sex with men (MSM) and, increasingly, heterosexual transmission.⁴⁴

HIV/AIDS also continues to increase among women. In 2004, the Joint United Nations Programme on HIV/AIDS estimated that nearly 40 million people were living with HIV/AIDS worldwide, with women accounting for nearly 50 percent of all cases.⁴⁵ In the United States, as of December 2003, women accounted for more than 18 percent (170,679) of the cumulative estimated number of 929,985 AIDS cases reported among adults and adolescents. In recent years, the incidence of AIDS has increased more rapidly among women than men. The proportion of new AIDS cases among women more than tripled from 1985 to 2002, from 7 percent to 26 percent. Fifty-three percent of HIV-infected women in the United States acquired HIV through heterosexual contact with HIV-infected men, and 42 percent through injection drug use. Also, HIV infection disproportionately affects minority women. Seventy-eight percent of HIV-infected women are African American and/or of Hispanic ethnicity, compared with only 52 percent of HIV-infected men.⁴⁶

NIAID's epidemiologic research explores the clinical course of and factors contributing to the transmission of HIV infection in a variety of populations. Groups of inner-city women and their children are the focus of the Women and Infants Transmission Study (WITS). Begun in 1990, WITS is a collaborative, multisite, longitudinal, natural history that has enrolled

more than 2,000 HIV-infected pregnant women and has followed post-partum mothers and their children. (For more information about WITS, see: <http://www.niaid.nih.gov/daids/wits.htm>.)

The Women's Interagency HIV Study (WIHS) includes both HIV-infected and uninfected women. The Multicenter AIDS Cohort Study (MACS) is a prospective, longitudinal study of HIV disease in homosexual and bisexual men. WIHS and MACS are the two largest observational studies of HIV/AIDS in women and homosexual or bisexual men, respectively, in the United States. Studies from these cohorts have repeatedly made major contributions to understanding how HIV is spread, how the disease progresses, and how it can best be treated. WIHS and MACS have completed their expansion to increase the size of the study groups by 60 percent and increase the number of minority participants. WIHS has expanded with an increase greater than 100 percent of the initial target enrollment. The expanded cohorts will focus on contemporary questions regarding HIV infection and treatment. (For more information about WIHS, see: <http://www.niaid.nih.gov/reposit/WIHS.htm>.)

WIHS researchers have published more than 250 peer-reviewed articles covering a wide scope of scientific research including the natural history of HIV infection; the impact of opportunistic infections and co-infections; the value of HIV viral load and CD4+ cell counts as markers of the success of highly active antiretroviral therapy (HAART); clinical outcomes of HAART therapy; the identification of biological, psychosocial and behavioral risk factors; the impact of aging and hormonal factors; the study of HIV-associated malignancies, particularly cervical cancer caused by the human papillomavirus; the analysis of gender differences in HIV disease; and the development of novel methods for analyses of cohort data. In addition, the cohort has provided an invaluable repository of clinical specimens and accompanying demographic and epidemiologic data to be used

for retrospective hypothesis testing. Currently, the WIHS is evaluating the cardiovascular manifestations of HIV among women.



A healthy minority woman expecting a healthy baby.

Mother-to-child transmission (MTCT) of HIV—which can occur during pregnancy, childbirth, or through breastfeeding—accounts for more than 90 percent of all cases of childhood HIV infection, especially in countries where effective antiretroviral drugs are not available. As more women of childbearing age become infected, the number of children infected with HIV also is expected to rise.⁴⁷ Efforts to prevent MTCT by targeting both the infant and the mother are being examined by the HIV Prevention Trials Network (HPTN) and the Pediatric AIDS Clinical Trials Group (PACTG), two NIAID-funded networks that support both domestic and international clinical research. Data from a NIAID-funded study that began in November 1997 in Uganda showed that the initial benefit to infants who, along with their mothers, received one dose of nevirapine, was sustained by the group of children until they reached age 18 months. These findings indicate

that short-course nevirapine effectively and safely reduces MTCT of HIV and, because of its low cost and ease of administration, provides an important alternative in resource-poor developing countries. Final followup for this study is completed, and data analysis is ongoing. (For more information about the HPTN, see: <http://www.niaid.nih.gov/factsheets/hptn.htm>.)

NIAID continues to support other research on gender-specific issues in HIV treatment through the Adult AIDS Clinical Trial Group (AACTG). Several studies have been initiated through the AACTG to examine, among other research questions, the pharmacokinetics of contraceptives in the setting of HAART; the use of antiretroviral therapy in pregnancy; gender differences in responses to HAART among treatment-naïve patients; toxicities and complications of different treatment regimens for HIV and HIV co-infections, such as human papillomavirus; metabolic complications of HAART; and changes in immunologic responses during postpartum. (For more information about the AACTG, see: <http://aactg.s-3.com/index.htm>.)

The HIV Vaccine Trials Network (HVTN) is an international network dedicated to developing HIV vaccines through testing and evaluating candidate vaccines in clinical trials. The HPTN also conducts clinical trials of nonvaccine HIV prevention strategies, including topical microbicides and MTCT studies, to develop and evaluate simple and less costly prevention regimens suitable for global use. MTCT studies also are carried out in the PACTG. Both HVTN and HPTN have initiated community outreach programs to educate people about HIV vaccine and prevention research and to encourage participation in clinical trials. Through these outreach activities, HVTN and HPTN researchers enroll in their clinical trials a diversified population that includes minorities and women. (For more information about the HVTN, see: <http://www.niaid.nih.gov/daids/vaccine/clinical.htm>.)

One of the greatest challenges facing HIV/AIDS researchers today is the recruitment and retention of minorities and women for clinical trials. As the epidemic continues to expand in minority communities, inclusion of these individuals in clinical trials is particularly urgent to ensure that the results of research are applicable to all populations affected by the disease. In October 2003, NIAID hosted a conference, “Increasing Diversity in Clinical Trials: Best Practices,” to explore the most effective strategies for recruiting minorities and women in clinical trials. (For more information about the conference, see: <http://www.niaid.nih.gov/healthdisparities/hdsymposium/proceedings2>.)

Also, to address the issues of recruiting and retaining minorities and women for clinical trials, NIAID released a new program announcement (PA), “Enrolling Women and Minorities in HIV/AIDS Research Trials,” to fund innovative approaches to reach, enroll, and retain women and racial/ethnic minorities in HIV/AIDS research trials in the United States. The PA will support projects to increase the number of women and minorities who participate in clinical trials for HIV/AIDS, relative to the incidence data, and will advance the body of scientific knowledge to improve the diagnosis, treatment, and development of preventive strategies in women and minorities. Additionally, each of NIAID’s large, multicenter therapeutic clinical trials networks, namely, the AACTG, PACTG, and the Terry Beirn Community Programs for Clinical Research on AIDS strives to ensure enrollment of a sufficient proportion of minority subjects.

NIAID is currently in the third year of its HIV Vaccine Communications Campaign (HVCC), which is aimed at developing and implementing a national education campaign to increase awareness of and support for HIV vaccine research, especially in at-risk populations such as African Americans, Hispanics, and MSM. The Division of Acquired Immunodeficiency Syndrome receives input and guidance for developing appropriate and culturally

sensitive messages from the HIV Vaccine Communications Steering Group, which includes representatives from community groups, other Federal agencies, pharmaceutical companies, and HIV vaccine advocacy groups.

A national survey was conducted to assess the attitudes and knowledge of HIV vaccine research in the general population as well as in segmented groups of African Americans, Hispanics, and MSM. According to data submitted for publication, 47.1 percent of African Americans, 26.5 percent of Hispanics/Latinos, and 13.4 percent of MSM believe an HIV vaccine already exists and is being kept secret; 22.0 percent of African Americans and 23.6 percent of the general public are aware that vaccines being tested cannot cause HIV infection; and 34.9 percent of African Americans and 28.8 percent of the general population support HIV vaccine trial volunteerism. These results indicate that misinformation and distrust continue to present formidable barriers to support for HIV vaccine research, and low public awareness and knowledge of HIV vaccine research must be addressed in order to develop and sustain HIV vaccine clinical research efforts. The HVCC is working to correct these misperceptions and to provide accurate information about HIV vaccine research.

Another major activity of the HVCC is to coordinate activities surrounding HIV Vaccine Awareness Day (HVAD), last held May 18, 2004. HVAD was established as a day to acknowledge and thank all the volunteers and researchers involved in HIV vaccine research. Community activities and media events around the country highlight research advances, address challenges associated with HIV/AIDS, recognize volunteers who have participated in HIV vaccine clinical trials, underscore why preventive HIV vaccines will offer the best hope for controlling the AIDS pandemic, and recognize the need for education. (For more information about HVAD, see: www.niaid.nih.gov/newsroom/mayday/default.htm.)

In FY 2004, the HVCC, through its contract with Ogilvy Public Relations Worldwide, awarded subcontracts to 8 national and 20 community organizations as part of the Community Education and Outreach Partnership Program (CEOPP). The CEOPP was designed to create local and national partnerships aimed at increasing the campaign's ability to provide messages to high-risk populations, specifically African Americans, Hispanics/Latinos, and MSM; ensure the inclusion of HIV vaccine research information in prevention, care, and treatment programs; eliminate myths, misconceptions, misperceptions, and misinformation relating to HIV prevention vaccine research; and measure the effectiveness of campaign messages.

An additional challenge is the recruitment of underrepresented minority investigators to AIDS and AIDS-related clinical and basic research disciplines. To address this challenge, NIAID supports a comprehensive portfolio of biomedical and behavioral research aimed at preventing and treating HIV disease in minority communities, training minority investigators, and fostering infrastructure development. NIAID continues to co-fund, with the National Center for Research Resources, the Research Centers in Minority Institutions (RCMIs) program by providing support for HIV/AIDS research pilot projects as well as infrastructure development at RCMIs. In FY 2004, NIAID awarded projects to seven institutions for research in diverse areas such as clinical, molecular, and vaccine development; drug development; opportunistic infections; immunology; and two comprehensive centers for health disparities.

In addition, NIAID awards grant supplements under the Research Supplements for Underrepresented Minorities (RSUM) program. The purpose of RSUM is to attract underrepresented minority investigators into biomedical and behavioral research. The supplements are made to NIAID-funded grantees to recruit and support investigators

interested in a particular area of scientific research. The awards are made on behalf of postdoctoral candidates, graduate students, faculty members, undergraduates, and reentry and disabled investigators. Several of the NIAID-sponsored Centers for AIDS Research also have a significant commitment to educating and training minority investigators and providing outreach to minority communities.

Sexually Transmitted Infections. Sexually transmitted infections (STIs) are critical global and national health priorities because of their devastating impact on minorities, women, and infants and their causal association with HIV infection. STIs are widespread, with 19 million new cases estimated to occur each year in the United States.⁴⁸ Several STIs, including genital herpes, gonorrhea, chlamydia, and syphilis, have higher incidences among minorities than among Whites in the United States.⁴⁹

Symptoms of STIs in women can be minor or nonspecific, especially in the early stages, and are often not diagnosed until late in the disease. STIs that occur during pregnancy can affect the fetus or newborn. About one-quarter to one-half of women infected with an STI during pregnancy gives birth to either premature or low birth weight infants. In about one-third to two-thirds of these pregnancies, the infection is passed to the infant and can cause permanent disabilities. Chlamydia, gonorrhea, and other infections of a woman's upper reproductive tract also can complicate pregnancy.

Chlamydia is the most commonly reported sexually transmitted bacterial disease in the United States, with an estimated 3 million new cases each year. The rate of reported infection with *Chlamydia trachomatis* is greater among women than men, and is particularly high in adolescent women. In women, chlamydial infections can cause pelvic inflammatory disease, which is a major cause of infertility, ectopic pregnancy, and chronic pelvic pain.⁵⁰ NIAID is currently planning to conduct a three-site trial

in Madagascar to test the effectiveness of the diaphragm to prevent chlamydial and gonococcal infection in women. This study is scheduled to begin in early 2005.

Genital herpes affects at least 45 million people in the United States. About 1 in 5 adults in the United States has genital herpes, but only one-third of these people know they have the virus. Although most genital herpes cases present no symptoms, asymptomatic individuals can transmit herpes simplex virus (HSV type 1 or 2) to others, and a pregnant woman infected with HSV can transmit the virus to her baby.⁵¹ NIAID is investigating treatments for herpes, including antiviral drugs and monoclonal antibodies, as well as studies to assess the role of antiviral suppressive therapy and vaccination in decreasing herpes transmission. In FY 2003, NIAID launched a pivotal phase III double-blind clinical efficacy trial of Herpevac, an investigational vaccine for the prevention of genital herpes in women ages 18 to 30. This trial, called the Herpevac Trial for Women, has expanded from 25 sites to 35 sites across the United States and is being conducted as a public-private partnership with GlaxoSmithKline, utilizing NIAID clinical sites. (For more information about the Herpevac Trial for Women, see: <http://www.niaid.nih.gov/dmid/stds/herpevac/default.htm>.)

Group B Streptococcus (GBS) is another infectious bacterium that is harmful to women and can be passed to their unborn children; it is the most common cause of life-threatening infections in newborns. Approximately 25 percent of pregnant women carry GBS bacteria in their vagina or rectum, although most women do not experience symptoms.⁵² NIAID is currently supporting a GBS vaccine research study called the Streptococcal Prevention in Non-Pregnant Women Study to determine whether a single vaccination with an investigational GBS type III vaccine can prevent non-pregnant women from acquiring GBS type III bacteria in their reproductive tract. There are several types of GBS;

type III is being studied because it is common in newborn infections.

Syphilis is caused by *Treponema pallidum*, a bacterium that is most commonly transmitted through sexual activity. It is possible for pregnant women with the disease to pass the bacterium to their unborn children, which can cause serious mental and physical disorders. Although the number of cases of syphilis is declining in the United States, in 2002, young women 20 to 24 years of age and men 35 to 39 years of age had the highest incidence of syphilis.⁵³ The NIAID-supported STD Clinical Trials Unit is currently conducting a randomized phase III trial to evaluate the equivalency of oral azithromycin versus injectable benzathine penicillin for treatment of primary syphilis. If successful, this could provide an additional antimicrobial strategy for treatment of this difficult disease.

Trichomoniasis is also common in the United States. Trichomoniasis is caused by a single-celled protozoan parasite called *Trichomonas vaginalis*. Although this common STI affects both women and men, symptoms are most common in women, with the highest incidence of this disease (in the United States) occurring in women between the ages of 16 and 35.⁵⁴ The NIAID-supported STD Clinical Trials Unit recently completed a multisite clinical study to determine the concordance of trichomoniasis between male and female partners. Researchers plan to publish these results in the near future.

NIAID has created an extensive infrastructure for conducting basic and applied research on STIs, including the STI Cooperative Research Centers, the STI Clinical Trials Unit, and the Topical Microbicides Program projects. These activities are part of an overall Institute effort to initiate and support a variety of other research projects that focus on: (1) developing vaccines, topical microbicides, and treatments for the microbes that cause STIs; (2) developing better and more rapid diagnostics; (3) sequencing the genomes of sexually transmitted pathogens; and

(4) understanding the long-term health impact of sexually transmitted pathogens in various populations. (For more information about the NIAID research program on sexually transmitted diseases, see: <http://www.niaid.nih.gov/dmid/stds>.)

The NIAID Topical Microbicides Program could be particularly important for protecting the health of women and children. A topical microbicide is a preparation (e.g., gel, cream, or foam) that is applied to the vagina or rectum to inactivate or inhibit STI pathogens, including HIV, that are being transmitted by either sexual partner. The majority of these infections are acquired through sexual intercourse, which underscores the need for developing a safe, effective, topically applied chemical and/or biologic barrier to prevent sexually transmitted HIV infection. Effective topical microbicides also might help prevent many other STIs. The ideal microbicide would be safe and nonirritating to the mucosal tissues, even if used on multiple occasions in a short period of time; inexpensive and unobtrusive; and available in both spermicidal and nonspermicidal formulations, so that women would not have to put themselves at risk for acquiring HIV and other STIs in order to conceive a child.

Transplantation. Transplantation represents a key health disparity for African Americans, who are at an increased risk for end-stage organ failure and the need for transplant. Despite a disproportionate representation on organ transplant waiting lists (27.1 percent of the total and 35.4 percent of kidney waiting list candidates), African Americans comprised only 18.2 percent of transplant recipients in 2003. In contrast to these disparities, African Americans, who make up approximately 13 percent of the U.S. population, accounted for 13.3 percent of all donors in 2003. (For more information about data on transplantation, see: <http://www.optn.org/data>.)

For reasons that are not well understood, African Americans experience lower survival rates after transplantation and higher incidences

of acute graft rejection and long-term immunosuppression-related adverse effects than do Whites. These disparities could be related to genetic factors, immunological factors, differences in drug pharmacokinetics, access to healthcare, socioeconomic factors, and medical noncompliance. To clarify the genetic factors that result in variable graft survival among populations, NIAID and the NIDDK launched the Genomics of Transplantation Cooperative Research Program in FY 2004. Researchers in this program will examine genetic polymorphisms and gene expression patterns in order to understand and predict transplant outcomes in diverse populations.

For kidney transplantation, matching of histocompatibility antigens (proteins that are the major targets of immune-mediated graft rejection) between donors and recipients is a consideration in prioritizing the distribution of organs. Because of racial or ethnic differences in the frequency of alleles (variants of a gene) at human leukocyte antigen (HLA) loci, African Americans are less likely to find a good match in the donor kidney pool than are candidates from other racial or ethnic groups, and the rate of graft failure is proportional to the level of mismatching.⁵⁵ These findings also apply to bone marrow transplantation, where HLA mismatching increases the risk of graft failure and graft versus host disease.⁵⁶ To increase knowledge of HLA diversity and improved donor-recipient matching, NIAID supports research to identify new HLA alleles in distinct racial and ethnic groups. NIAID-supported researchers have discovered 13 new HLA alleles in African Americans, 3 new alleles in Native Alaskan Yup'iks, and 2 new alleles in Lakota Sioux. In addition to facilitating improved donor-recipient matching in organ and hematopoietic stem cell transplantation, this research may provide additional insights into the origin and diversity of humans. (For more information about policies related to matching organ donors and recipients,

see: <http://www.optn.org/policiesAndBylaws/policies.asp>.)

Tuberculosis. Tuberculosis (TB), which is caused by the bacterium *Mycobacterium tuberculosis* (*M. tb*), is one of the leading causes of illness and death in the world, and kills more people than AIDS and malaria combined. The World Health Organization estimates that approximately one-third of the world's population is infected with *M.tb*, approximately 8 million new TB cases occur annually, and 2 million people die each year from TB.⁵⁷

TB also remains a public health concern in the United States. The CDC estimated that 5 to 10 percent of the U.S. population (14 to 28 million persons) was infected with TB and in 2003, and 14,871 new TB cases occurred in the 50 States and the District of Columbia.⁵⁸ The disease persists disproportionately among racial/ethnic minority populations in the United States. During 2003, approximately 53.3 percent of the reported active TB cases in the United States were among foreign-born persons. Within minority populations, the largest number of reported TB cases occurred in non-Hispanic Blacks (45 percent of minority cases).⁵⁹ Combined factors such as urban poverty, high HIV infection rates, and the effects of household crowding might contribute to the disproportionate impact of TB on minorities. Also, the rise of multidrug-resistant strains of TB and co-infection with HIV has further extended the impact of TB in the United States and around the world.

Over the past decade, dramatic increases in NIAID funding for TB research have allowed the Institute to support a wide range of TB initiatives and to increase the community of TB researchers. In FY 2004, NIAID awarded a contract to Colorado State University to continue to provide TB research reagents to qualified investigators throughout the world, enabling them to work with consistent, high-quality microbiological, immunological, and genomic

reagents. This contract will also enable exploratory and preclinical evaluation of promising new TB vaccine candidates in state-of-the-art animal models. NIAID also continues to support international clinical studies of TB/HIV co-infection, with active Institute program staff participation on projects in Africa, Asia, and South America. A high-priority goal of the Institute's research program is the development of improved TB vaccines.

In addition, NIAID continues to support the Tuberculosis Research Unit at Case Western Reserve University, which conducts multidisciplinary laboratory and clinical studies to answer critical questions about human TB; provides knowledge, tools, and technologies to improve TB clinical trials; and offers the ability to conduct clinical studies for the evaluation of new or improved vaccines, therapeutics, and diagnostics. (For more information about the Tuberculosis Research Unit at Case Western Reserve University, see: www.tbresearchunit.org.)

Minority Researchers' Training Programs

Increasing the participation of underrepresented minority investigators in virtually all fields of biomedical research is a continuing NIH and NIAID priority. In addition to supporting NIH-wide programs, NIAID has developed and supported a variety of innovative minority programs for biomedical research, encompassing high school through postdoctoral training.

In FY 2004, NIAID continued its extramural arm to its longstanding Introduction to Biomedical Research Program. The Richard M. Asofsky Scholars In Research (ASIR) award was created to represent and honor Dr. Asofsky's dedication to bringing underrepresented minorities into the biomedical sciences. The ASIR program provides supplemental funding to NIAID extramural principal investigators for the purpose of supporting underrepresented minority high school and college students in their research

laboratories and to expose them to research career opportunities in the areas of allergy, immunology, transplantation, microbiology, and infectious diseases, including AIDS. These NIAID ASIR awards are used to encourage the development of underrepresented minority researchers as outlined in the NIAID *Strategic Plan on Health Disparities*. (For more information about the Richard M. Asofsky Scholars In Research award, see: <http://grants2.nih.gov/grants/guide/pa-files/PA-03-071.html>.)

In FY 2004, NIAID announced an initiative, Enhancement Awards for Underrepresented Minority Scientists, to solicit applications from underrepresented minority investigators who are in the early stages of their scientific careers (assistant professor or junior-level faculty) to establish basic or clinical research programs in the areas of allergy, immunology, transplantation, microbiology, and infectious diseases, including AIDS. The goals of the program are to increase the number of underrepresented minority investigators performing independent, competitive research in the areas encompassed by NIAID's scientific mission and to enhance the long-term research skills and potential of these individuals. NIAID received 57 applications under this initiative. (For more information about the Enhancement Awards for Underrepresented Minority Scientists, see: <http://grants1.nih.gov/grants/guide/rfa-files/RFA-AI-03-045.html>.)

Since 1993, NIAID has conducted a symposium designed for recipients of the Research Supplements for Underrepresented Minorities to encourage them to continue studies related to NIAID's biomedical research agenda. In November 2003, NIAID held its sixth Bridging the Career Gap for Underrepresented Minority Scientists symposium with 70 attendees. (For more information about the symposium, see: http://www.niaid.nih.gov/osprt/bridging_the_career_gap.htm.)

In February 2004, NIAID's Division of Intramural Research (DIR) Office of Training

and Special Emphasis Programs (OTSEP) held its second annual outreach program for underrepresented minorities in the biomedical sciences. This 5-day program on Intramural NIAID Research Opportunities (INRO) included scientific lectures by NIAID researchers, discussions with scientists, and tours of the Research Technologies Branch and the Vaccine Research Center (VRC). Three key features distinguish this new program and will result in more minority students participating in intramural training programs at all levels. Eventually, this programmatic strategy will create a larger pool of potential candidates for career positions in NIAID. First, the selection of students is based on academic excellence, interest in NIAID research, and desire to participate in NIAID's DIR training programs. Second, current DIR minority trainees are included in all aspects of the program and are invited to give presentations. This allows the visiting students to see first-hand what can be accomplished and to network with the trainees. Third, all participants will be tracked in future years to inform them about NIAID training and professional opportunities and to enlist their participation in OTSEP's outreach activities.

In FY 2004, the OTSEP Underrepresented Minority Programs were fully subscribed for the postbaccalaureate Intramural Research Training Awards (IRTA) traineeships; the first minority graduate student was selected for OTSEP sponsorship; one female postdoc, recruited from the University of Virginia, began her 2-year sponsorship; and three minority postdocs continued their research in DIR and one in the VRC. Upon completion of their DIR training, most OTSEP-sponsored trainees begin graduate or medical school.

A nationwide marketing strategy proved highly successful in promoting INRO 2004. Historically Black colleges and universities were targeted for outreach. As a result of these activities, the number of qualified applicants increased, and 10 INRO 2004 participants were offered training

positions in DIR labs—postbaccalaureate IRTA and Summer Internship Program. Eight of these students have begun their laboratory traineeships.

Another program in which NIAID staff members participate, the Summer Medical Education Program, is sponsored by the Robert Wood Johnson Foundation and is targeted to minority students who plan to attend medical school. In FY 2003, 400 students at the Case Western Reserve University, University of Virginia, and Yale University Student Medical Education Program attended presentations to learn about INRO 2005 and DIR training opportunities. (For more information about the Summer Medical Education Program sponsored by the Robert Wood Johnson Foundation, see: <http://www.rwjf.org/portfolios/resources/grant.jsp?id=050019&iaid=135>.)

Research Guidelines

In all clinical research, including biomedical and behavioral studies, NIAID complies with the 1993 NIH *Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research*. Congress mandated the establishment of these guidelines in the NIH Revitalization Act of 1993, and NIAID staff members participated in their development. The guidelines stipulate that women and members of minority groups must be included in all NIH-supported research projects involving human subjects, unless there is a compelling reason that such inclusion would be inappropriate. The guidelines also state that women of childbearing potential should not be routinely excluded from participation in clinical research.

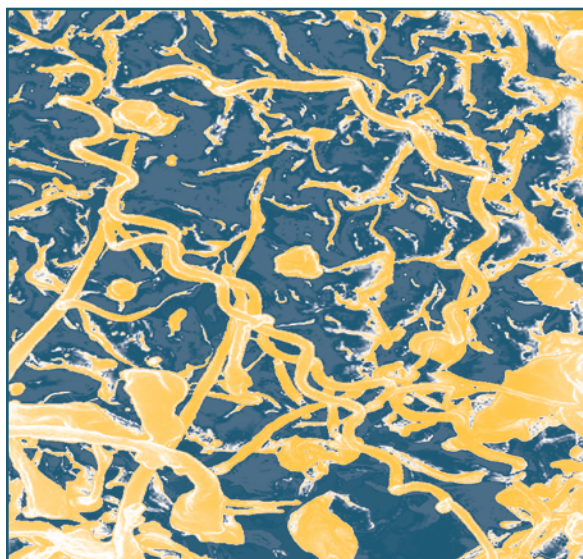
SEXUALLY TRANSMITTED INFECTIONS

Sexually transmitted infections (STIs), also commonly referred to as sexually transmitted diseases (STDs), are critical global and national health priorities because of their relationship with HIV/AIDS and the devastating impact they have on women and infants. In the United States, more than 65 million people are living with an incurable STI, and an estimated 15 million people become infected with at least one STI annually, approximately one-half of whom contract infections that will affect them for the rest of their lives.⁶⁰

A number of conditions can occur later as a consequence of having STIs, including infertility, tubal pregnancy, cervical cancer, fetal wastage, low birthweight, congenital or perinatal infection, and other chronic conditions such as neurosyphilis. Moreover, substantial biological evidence demonstrates that the presence of other STIs increases the likelihood of both transmitting and acquiring HIV. Recent studies indicate that the more prevalent nonulcerative STIs (chlamydia infection, gonorrhea, bacterial vaginosis, and trichomoniasis) and ulcerative diseases (genital herpes, syphilis, and chancroid) increase the risk of HIV transmission by at least twofold to fivefold.⁶¹

NIAID supports research for more effective prevention and treatment approaches to control STIs. These approaches include (1) the development and licensure of vaccines, topical microbicides, and treatments for the microbes that cause STIs; (2) understanding the long-term health impact that sexually transmitted pathogens have in various populations; (3) stimulating basic research on the pathogenesis, immunity, and structural biology of these pathogens; and (4) developing better and more rapid diagnostics.

To carry out these activities, NIAID supports a broad STI research portfolio (www.niaid.nih.gov/dmid/stds), which addresses these diseases through individual investigator-initiated research grants, contracts, and a variety of research programs. Among these programs are the STD Cooperative Research Centers, which bridge basic biomedical, clinical, behavioral, and epidemiologic research; promote productive collaborations among academic researchers; and facilitate the development of intervention-oriented research. This program, which is currently being recompeted, has been broadened to include topical microbicides. Another program, the STD Clinical Trials Unit, conducts clinical trials to test the safety and efficacy of biomedical and behavioral interventions aimed at the prevention and control of STIs. The Topical Microbicides Program conducts basic research, product development, and clinical evaluation activities aimed at developing female-controlled barrier methods for the prevention of HIV/AIDS and other STIs.



Treponema pallidum, the organism that causes syphilis.

NIAID also supports the sequencing of the genomes of sexually transmitted pathogens, including *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Haemophilus ducreyi*, *Treponema pallidum*, and *Ureaplasma urealyticum*. This information has provided new insights into the pathogenesis of numerous STIs and is paving the

way for development of new diagnostics, drugs, vaccines, and microbicides.

In fiscal year 2004, NIAID continued to support and encourage the development and evaluation of STI diagnostics designed for point-of-care use through the Small Business Innovation Research mechanism. NIAID also is supporting a clinical trial to compare a new oral antibiotic treatment regimen with the one currently recommended for the treatment of primary syphilis. Results from this trial could provide an alternative treatment option.

Additional STI activities include the following:

- A pivotal phase III double-blind clinical efficacy trial of an investigational vaccine for the prevention of genital herpes. Launched in November 2002, this clinical trial has expanded from 25 sites to 35 sites across the United States and plans to enroll 7,550 women between the ages of 18 to 30. This study, which is called the Herpevac Trial for Women, is being conducted as a public-private partnership with GlaxoSmithKline. The trial is estimated to require 4 years to complete.
- Over the past 2 years, the STD Prevention Primate Unit for preclinical evaluation of topical microbicides and vaccines at the University of Washington has evaluated several candidate microbicides for safety (effects on surface tissues and microenvironment of the cervix and vagina) in pig-tailed macaques. Results from this Division of Microbiology and Infectious Diseases (DMID)-supported testing contract are being coordinated with testing conducted by the Division of Acquired Immunodeficiency Syndrome to facilitate product development and safety and efficacy testing in clinical trials.
- The STD Clinical Trials Unit has completed a multisite clinical study to determine the

concordance of trichomoniasis between male and female partners. A manuscript for publication of data is being written.

- A protocol has been developed to conduct a three-site trial in Madagascar testing the effectiveness of the diaphragm to prevent chlamydia and gonococcal infection in women. The study is scheduled to begin in early 2005.
- The Sexually Transmitted Infections Clinical Trials Group (STI CTG) was awarded two new contracts in September 2004. The STI CTG will provide an infrastructure to conduct clinical trials to test the safety and efficacy of interventions aimed at the prevention or control of STIs and to support clinical studies to assess the feasibility and accuracy of diagnostic and screening tests.

Topical Microbicides

NIAID continues to focus a great deal of its prevention efforts on the development of virus- and bacteria-killing gels, foams, creams, or films, known as topical microbicides, as a means of protecting against sexual transmission of HIV and other STIs.

Topical microbicides work by killing HIV or other sexually transmitted pathogens or by creating a barrier that prevents them from entering or binding to cells. Ideally, microbicides would be unnoticeable, fast-acting against HIV and a broad range of other sexually transmitted pathogens, inexpensive, safe for use at least one to two times daily, and easy to store. Microbicides with and without contraceptive properties are needed so that a woman's reproductive decisions do not affect her risk for HIV/STI infection. In addition, microbicides may provide protection to men who have sex with men.

NIAID's research effort for developing topical microbicides includes basic research, preclinical product development, and clinical evaluation. The goal of this comprehensive effort is to

support research and development that leads to the identification of safe and effective topical microbicides. NIAID's Strategic Plan for Topical Microbicides, a document that provides a detailed, long-range plan for advancing microbicide concepts from the laboratory to clinical trial evaluation was officially released this past year and can be found at: www.niaid.nih.gov/publications/topical_microbicide_strategic_plan.pdf.

A number of NIAID-sponsored programs solicit for topical microbicide research. These include the Innovation Grants for AIDS Research Program, the Integrated Preclinical/Clinical Program for HIV Topical Microbicides (IPCP-HTM) and the HIV Microbicide Design and Development Team. The Innovation Grant Program stimulates new, scientifically challenging, and untested ideas in AIDS research, with a particular focus on microbicide research. The IPCP-HTM focuses on iterative preclinical and clinical research for novel microbicide strategies against HIV infection. The overall goal is to encourage advanced optimization and development of new and pioneering topical microbicide candidates and combinations and to foster translation of new microbicides/combinations from preclinical studies to pilot clinical studies in order to segue these studies into large safety and efficacy clinical trials within the HIV Prevention Trials Network. These new awards significantly expand the scope of the IPCP-HTM to introduce programs focusing on development of combination inhibitors using dendrimer platform technology, rectal microbicide development, and delivery strategies using engineered *Lactobacilli*. The HIV Microbicide Design and Development Teams is a milestone-driven contract program designed to streamline development of microbicide candidates, emphasizing combination products with multiple active agents. Initiation of a phase I safety trial is required within the award period. The first of these contracts will be awarded in 2005.

This past year, NIAID awarded a Master Contract for Preclinical Development to help identify potential new microbicide candidates and provide all support needed for small-scale production and packaging, preclinical testing, and documentation leading to Investigational New Drug submission for phase I clinical testing.

NIAID supports large-scale *in vitro* screening of potential HIV transmission-blocking agents through a contract with Southern Research Institute in Frederick, Maryland. Potential microbicides from the private sector and from academic and government sources are tested in several different assays that mimic the vaginal environment to determine their ability to block HIV transmission from infected T cells to cultures of cells lining the human cervix. In the past year, 345 compounds were tested.

Microbicide development also is supported through a DMID contract with the University of Washington. During the past year, several candidate microbicides were evaluated for safety (effects on the surface tissues and microenvironment of the cervix and vagina) in nonhuman primates. Results from these and other testing efforts will be coordinated to facilitate product development and safety and efficacy testing in clinical trials.

Several promising topical microbicide candidates are in various stages of clinical testing. BufferGel® is an acid-buffering gel that helps maintain the normal acidic environment of the vagina during coitus to disrupt the transmission of acid-sensitive sexually transmitted pathogens such as HIV. Results from clinical trials through NIAID's HIV Prevention Trials Network (HPTN) in the United States, India, Thailand, Zimbabwe, and Malawi found BufferGel® to be safe and well-tolerated in uninfected women and men.

The HPTN studies of PRO 2000/5 gel, a synthetic compound that works by inhibiting HIV entry, were completed recently in the United

States and Durban and Johannesburg, South Africa, among sexually active women who were at low risk of HIV infection and in sexually abstinent asymptomatic HIV-infected women. PRO 2000/5 gel was found to be well-tolerated at different concentrations.

Now that studies of PRO 2000/5 gel and BufferGel® have shown that they are both safe and well-tolerated, NIAID is planning a phase II/IIb study, called HPTN 035, to further evaluate the safety and effectiveness of these compounds in preventing HIV infection in women. To further prepare for the implementation of HPTN 035, an HIV prevention preparedness study also has been initiated at four international HPTN sites in Zambia, South Africa, and Tanzania. This study will assess the ability of sites to recruit and retain participants for future efficacy trials

of topical microbicides and to develop reliable data on HIV seroprevalence and seroincidence in the target populations. This study is currently enrolling patients.

This past year, three phase I clinical trials of topical microbicide candidates were completed. They were A Phase I Safety and Acceptability Study of the Investigational Vaginal Microbicide PRO2000/5 Gel (P) (HPTN 047); A Phase I Safety and Acceptability Study of the Vaginal Microbicide 6% Cellulose Sulfate Gel Among HIV-Infected Women (HPTN 049); and A Phase I Safety and Acceptability Study of the Vaginal Microbicide Agent PMPA Gel (HPTN 050). In all three trials, the products were found to be safe and acceptable by participants as well as their sexual partners (where relevant).

TRANSPLANTATION

Transplantation of organs, tissues, and cells has become a powerful mode of treatment for dozens of life-threatening diseases affecting millions of Americans. Today, doctors routinely transplant more than 25 different organs and tissues to treat kidney failure, type 1 diabetes, leukemia, end-stage pulmonary disease, liver disorders, cardiovascular disease, and many other disorders.

Two major impediments to successful transplantation remain, however. The first of these is immune system rejection. Recent research advances have provided a much clearer understanding of the immune mechanisms that cause graft rejection. These insights have in turn led to better therapies to suppress the immune system, and thereby allow a graft to survive and function. As a result, 1-year graft survival rates have increased for all organs and tissues, and in many cases now exceed 80 percent. But despite this improvement, long-term graft survival rates have not increased nearly as much.

The second barrier to wider use of transplantation is a critical shortage of donor organs and tissues. Nationwide, there are more than 87,000 candidates on waiting lists for organ transplantation: 59,737 for kidneys; 17,462 for livers; 4,076 for pancreas or combined kidney/pancreas transplants; 3,576 for hearts or heart-lung transplants; and 3,946 for lung transplants.⁶² This demand far outstrips the supply of donor organs in the United States. In 2003, 13,280 individuals were organ donors; for the third consecutive year, most of these were living donors.⁶³ Unfortunately, many candidates die while awaiting a suitable organ.

Immune-Mediated Graft Rejection

To further improve both short- and long-term graft survival, the NIAID Division of Allergy, Immunology, and Transplantation (DAIT) supports a broad portfolio of basic research in transplantation immunology, as well as preclinical

evaluation and clinical trials of promising post-transplant therapies. The major goals of DAIT's transplantation research program are to understand the pathways whereby the immune system recognizes transplanted organs, tissues, and cells; characterize the cellular and molecular components of acute rejection and chronic graft failure; evaluate novel therapies for treating rejection and prolonging graft survival in preclinical models; develop and implement strategies for immune tolerance induction; and conduct clinical trials of new therapies to improve graft survival, while minimizing the toxic side effects of immunosuppressive drugs.

Kidney transplantation, which is the preferred therapy for end-stage renal disease, accounts for 59 percent of all solid organ transplants. In fiscal year (FY) 2003, NIAID renewed the Cooperative Clinical Trials in Pediatric Transplantation (CCTPT) program, first established in 1994. The goals of CCTPT are to support multicenter clinical trials of new ways to prevent graft rejection in pediatric kidney transplant patients, evaluate changes in drug regimens intended to limit side effects of immunosuppression, and assess pre-transplant immunotherapies. Ongoing CCTPT clinical trials include an evaluation of the immunosuppressive drug sirolimus for chronic graft failure, and a study of the effects of steroid withdrawal in pediatric transplant recipients. CCTPT also conducts immunological studies to determine how these various interventional approaches affect the immune system.

In FY 2004, NIAID collaborated with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the National Heart, Lung, and Blood Institute to establish a clinical consortium intended to improve the success of organ transplants. The goals of the consortium are to identify genetic factors in patients that could help doctors predict transplant outcomes, as well as responses to post-transplant therapy; to develop diagnostic tests that enable early detection and ongoing monitoring of immune-related processes; and to

test the safety and effectiveness of new, less toxic immunosuppressive drugs.

NIAID and NIDDK also cooperatively established the Genomics of Transplantation Cooperative Research Program to support interdisciplinary, large-scale genomic studies in clinical transplantation. The goals of the program are to understand the genetic factors that affect immune-mediated graft rejection and to provide a rational basis for the development of more effective strategies for long-term graft survival.

In FY 2003, NIAID launched a clinical trial of dietary supplements in kidney transplant recipients. Previous data suggested that extra arginine and omega-3 fatty acids in the diet might reduce the incidence of post-transplant infections, duration of hospital stays, and frequency of acute rejection episodes. The current trial is investigating the tolerability and safety of this dietary regimen, as well as its effect on post-transplant health. If it proves effective, this intervention could reduce healthcare costs and increase quality of life for transplant recipients.

Patients with HIV infection are at high risk for end-stage organ disease. Before the advent of highly active antiretroviral therapy (HAART), people with HIV were generally not considered for transplants because of their poor prognosis. HAART, however, has improved the outlook for HIV-positive patients so that many more HIV-positive patients with end-stage kidney and liver disease are potential transplant candidates. In FY 2003, DAIT and the NIAID Division of AIDS launched a clinical trial of the safety and efficacy of kidney and liver transplantation in patients with HIV.

Induction of Immune Tolerance

The drug regimens that suppress a patient's immune system usually can prevent graft rejection, but they also cause serious side effects such as infections and malignancies. Transplant immunologists, therefore, hope to

develop treatments that can both reduce these risks and improve graft survival. One promising alternative is to selectively modify the immune response to establish tolerance to the graft while leaving protective immune responses intact. In collaboration with NIDDK, DAIT in FY 2002 renewed and expanded the Nonhuman Primate Immune Tolerance Cooperative Study Group. This program evaluates novel regimens intended to induce transplant tolerance in animal models. Scientists working in the study group have already demonstrated that kidney and islet transplant patients given tolerogenic regimens have increased long-term graft acceptance. In FY 2005, the program will be expanded to include heart and lung transplantation. To accelerate the research conducted through this program, DAIT also supports breeding colonies of rhesus and cynomolgus monkeys.

With cosponsorship from NIDDK and the Juvenile Diabetes Research Foundation International (JDRF), NIAID supports the Immune Tolerance Network (ITN), an international consortium of more than 80 investigators in the United States, Canada, Europe, and Australia. This network clinically evaluates tolerance-inducing therapies for many immune-mediated disorders, including rejection of transplanted organs, tissues, and cells. ITN also conducts studies on the underlying mechanisms of these approaches and develops new ways to measure the induction, maintenance, and loss of immune tolerance in humans. Since its inception, ITN has established a variety of state-of-the-art core facilities, initiated more than 18 clinical protocols, and funded several basic science studies of the mechanisms of induced immune tolerance. More information on ITN is available at www.immunetolerance.org.

Shortage of Donor Organs

The number of organ transplants performed in the United States has increased dramatically, from 12,619 in 1988 to 25,466 in 2003.⁶⁴ These numbers would be even higher if more

donor organs were available; the waiting list for transplants has quadrupled since 1988. DAIT is addressing this problem by supporting efforts to improve donor registries that identify potential donors and by developing educational initiatives to increase public understanding of organ donation, especially among minority populations.

In collaboration with several NIH Institutes and Centers and the JDRF, NIAID supports the International Histocompatibility Working Group (IHWG). The IHWG is a network of more than 200 laboratories in more than 70 countries that collects and shares data on the human leukocyte antigen (HLA) gene complex, which determines the compatibility of donor organs and tissues. The goals of this program are to improve histocompatibility testing, find HLA types that are associated with autoimmune diseases, and improve donor-recipient matching for hematopoietic stem cell (HSC) transplantation. IHWG investigators have joined forces with HSC transplant centers to develop an international database of transplantation outcomes and donor-recipient HLA genotypes. This effort will help to determine optimal matching criteria for HSC transplants between unrelated people and increase access to this therapy for ethnically diverse populations. In addition, IHWG researchers are working to identify single nucleotide polymorphisms (SNPs) in immune-response genes. SNP variations may account for the increased susceptibility of certain

individuals or groups to immune-mediated diseases. To date, SNP data have been gathered for more than 100 genes related to immune responses.

The use of nonhuman organs, tissues, or cells in human transplantation, called xenotransplantation, is another strategy DAIT is pursuing to increase the supply of transplantable organs and tissues. The potential of xenotransplantation, however, is severely limited by the violent response of the human immune system to nonhuman tissues; concerns have also been expressed that infectious agents might inadvertently be introduced from animal donors into humans. DAIT-supported xenotransplantation research focuses on increasing our understanding of the human immune response to antigens present on cells from nonhuman species, and on the development of methods for rapid identification and treatment of any infectious diseases that might be caused by organisms present in animal donor tissue.

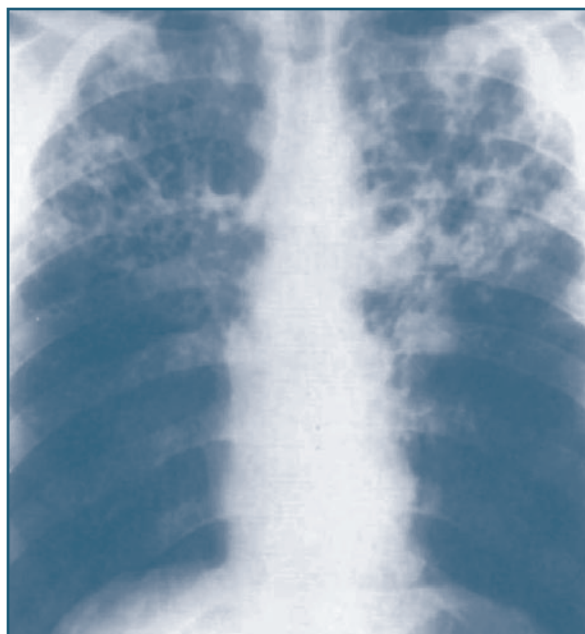
With each advance in transplantation, a new set of challenges emerges. The challenges facing transplantation are improving long-term graft survival, establishing long-term tolerance without immunosuppressive drugs, and reducing lengthy transplant waiting lists. NIAID's basic and clinical research programs in transplantation are committed to meeting these challenges.

TUBERCULOSIS

NIAID plays a lead role in the NIH tuberculosis (TB) research program. In response to ongoing concern about increasing worldwide case rates and the development of multidrug-resistant strains of *Mycobacterium tuberculosis* (*M.tb*), the pathogen that causes TB, NIAID has increased its TB research portfolio steadily over the past decade. The World Health Organization (WHO) estimates that there are approximately 8 million new TB cases annually, with 2 million deaths. This toll makes TB the leading cause of death from a single infectious pathogen worldwide, killing more people than AIDS and malaria combined. Approximately one-third of the world's population is infected with *M.tb*, and 1 in 10 of these individuals likely will develop active TB disease in their lifetimes. If current trends continue, an estimated 1 billion people will be newly infected by the year 2020; approximately 200 million people will develop active TB, and 35 million will die.⁶⁵

NIAID supports a broad TB research program, primarily through its extramural Division of Microbiology and Infectious Diseases (DMID), with particular emphasis on the following areas:

- Basic biology and pathogenesis of *M.tb*, host-pathogen interaction, and host response to TB in animal models and humans;
- Research into the various stages of TB, including persistent, asymptomatic infection with *M.tb* (latency), reactivation, and progression to TB;
- Development and testing of vaccines, chemotherapeutics, and diagnostics;
- Development of improved tools for epidemiologic studies; and
- Mycobacterial genomics and postgenomic analyses.



Lung showing lesions caused by infection with *Mycobacterium tuberculosis*.

Recent funding increases have allowed the Institute to support a number of initiatives and to markedly expand the community of TB researchers. Higher levels of funding enabled NIAID to establish the Tuberculosis Research Unit (TBRU) at Case Western Reserve University in 1994 (www.tbresearchunit.org). TBRU continues to make progress in developing surrogate markers of disease and human protective immunity, and in conducting clinical trials of potential new TB therapeutic, preventive, and diagnostic strategies. Activities of the TBRU are coordinated with other major organizations involved in TB research, including the Centers for Disease Control and Prevention, U.S. Agency for International Development, U.S. Food and Drug Administration (FDA), WHO, Global Alliance for TB Drug Development, and International Union Against Tuberculosis and Lung Disease, and with interested industrial partners.

NIAID's extramural TB research program currently supports more than 200 grants for basic, applied, and clinical TB research. Among the projects supported by NIAID is an award to The Institute for Genomic Research in Rockville, Maryland, to support sequencing and annotation

of *Mycobacterium smegmatis* (strain MC2 155), an important model system used in TB research. *M. smegmatis* microarrays are produced under this grant and were distributed through the Pathogen Functional Genomics Resource Center in FY 2004. For a current list of available microarrays, which includes *M. smegmatis*, see <http://www.niaid.nih.gov/dmid/genomes/pfgrc/guidelines.htm>. For access to genome data, see www.tigr.org/tdb/mdb/mdbinprogress.html.

The development of improved TB vaccines, which are crucial to the long-term control of TB worldwide, is a high priority. In December 2003, NIAID, together with the FDA Center for Biologics Evaluation and Research, sponsored a workshop to outline U.S. regulatory requirements for the development and human testing of new TB vaccines (<http://www.niaid.nih.gov/dmid/meetings/tbvacc.htm>). The NIAID Blueprint for TB Vaccine Development, presented at the 1998 International Symposium for Tuberculosis Vaccine Development and Evaluation, outlines the specific steps needed to develop improved TB vaccines (<http://www.niaid.nih.gov/publications/blueprint>). A Department of Health and Human Services-wide task force, which includes representation from NIAID, oversees implementation of the blueprint report. Clinical trials of two new TB vaccines that were developed with NIAID support began in 2004. One is a recombinant version of the bacillus Calmette-Guerin vaccine, developed by investigators at UCLA; the other is an adjuvant-peptide fusion vaccine developed by Corixa Corporation.

Through the Tuberculosis Research Materials and Vaccine Testing contract with Colorado State University, NIAID provides TB research reagents and preclinical vaccine testing services to qualified investigators throughout the world. By the end of FY 2004, more than 150 new TB vaccine candidates had been tested under this contract, one of which has recently entered human clinical trials with several others progressing through various stages of preclinical development.

Contracts issued by DMID and the Division of Acquired Immunodeficiency Syndrome (DAIDS) are used to support and promote a range of TB studies from basic through translational to applied research. Under the contracts, NIAID (1) offers *M.tb*-derived research reagents and animal model screening services for candidate TB vaccines (<http://www.cvmb.colostate.edu/microbiology/tb/top.htm>); (2) offers candidate compound identification and acquisition services, and in vitro and animal model screening services to evaluate drug candidates (<http://www.taacf.org>); (3) provides funding for the development of improved TB vaccines using already existing technology platforms; (4) supports TBRU to conduct multidisciplinary laboratory and clinical studies to answer critical questions about human TB; to provide knowledge, tools, and technologies to improve human clinical trials in TB; and to provide the capability to conduct clinical studies for the evaluation of new or improved vaccines, therapeutics, and diagnostics (<http://www.cwru.edu/affil/tbru/index.htm>); and (5) assists with technology transfer for potential commercialization of new drug discoveries for TB.

Under the NIAID contracts mentioned above, the Southern Research Institute maintains the Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF) to acquire drug candidates for screening against virulent *M.tb*, maintains a computerized chemical database of candidate structures, coordinates and distributes compounds for evaluation *in vitro* and in animal models, and reports data to compound suppliers. TAACF has contacted more than 3,500 chemists throughout the world seeking candidate anti-TB compounds. TAACF has received more than 70,000 compounds from academic and private-sector investigators, principally in the United States and Europe, with growing involvement of scientists from Africa, Asia, Australia, South America, and other regions.⁶⁶

NIAID supports a high-throughput, robotics screening contract that continues to provide

screening services to discover new antimicrobials. The facility supported under this contract provides the capability of testing large chemical libraries of compounds for activity against specific biochemical drug targets and against growing microorganisms. In addition to supporting *in vitro* evaluation of compounds from chemical repositories, DAIDS also recently awarded two research grants to stimulate preclinical research for novel therapeutic strategies against TB in the context of HIV/AIDS.

A new component of the NIAID TB drug-development support services was awarded in 2004 under the Pharmacokinetics and Pharmacodynamics Animal Model contract. This contract supports a central facility to identify and evaluate novel compounds for their basic pharmacology and efficacy characteristics, provide critical support for investigator-initiated drug discovery, stimulate private-sector sponsorship of new drugs, perform comparison and confirmatory studies from different sponsors, and provide information for the selection of antimicrobial drug candidates for designing clinical studies.

NIAID also participates in a newly formed public-private partnership—the Global Alliance for Tuberculosis Drug Development (<http://www.tballiance.org>)—together with WHO, the Rockefeller Foundation, and other international organizations dedicated to encouraging new therapeutic advances in the absence of industrial sponsorship. In addition, increased funding through Small Business Innovation Research grants has promoted development and evaluation of new tools for treating and preventing TB.

DAIDS is supporting clinical trials of new treatment and prevention strategies for tuberculosis in the setting of HIV/AIDS. These investigations are being conducted in countries with a high burden of disease associated with both TB and HIV. The interactions of these two infections are associated with high mortality, particularly in African nations. In 2004, DAIDS awarded one grant under the International

Studies of AIDS-Associated Co-infections program, which is designed to develop effective and sustainable clinical management strategies to improve care and foster integration of research on HIV and co-infection pathogens including tuberculosis. The Comprehensive International Program of Research on AIDS supports research studies addressing important public health research questions in high-burden countries.

The Division of Allergy, Immunology, and Transplantation (DAIT) supports a number of individual research projects concerned with basic mechanisms of immunity to *M.tb*. DAIT's research goals and objectives on *M.tb* are as follows:

- Understand how the immune system recognizes and responds to bacteria such as *M.tb*, hidden within host cells, and support research on antigen presentation and stress molecule induction as they relate to activation of cell-mediated immunity to intracellular pathogens;
- Promote vaccine-relevant research to identify dominant mycobacterial antigens and novel adjuvants that induce protective cellular immune responses;
- Promote research on the development of immunologic reagents for early diagnosis and monitoring of disease; and
- Support research on the identification of immune system genes that activate in response to mycobacterial infection, especially genes that encode soluble proteins that might be relevant to the development of TB vaccines or therapies.

Research topics include T-lymphocyte recognition of mycobacterial lipid antigens, the role of various cell populations in combating *M.tb* infection, and the function of biological oxidants in protective immune processes.

DAIT supports several projects that assist research on TB as well as other infectious diseases such as hepatitis C, malaria, and HIV. Under the Application of Data on Human Leukocyte Antigen (HLA) to the Improvement of Vaccines program, DAIT supports the HLA Ligand/Motif Online Database, a Web-based, searchable database of human major histocompatibility complex (MHC) molecules and peptide ligands. The database specifies amino acid sequences of peptides derived from viral, bacterial, parasitic, and human proteins in association with human class I or class II MHC molecules. This resource enables users to search for specific human MHC/peptide combinations or to determine ligand amino acid motifs that will facilitate their research. Support is provided under a NIAID contract to the University of Oklahoma.

The NIAID Tetramer Facility produces peptide-MHC reagents for T cell detection. Reagents this facility supplies are relevant to many vaccine-related topics, including intracellular bacterial, viral, and parasite infections; autoimmune diseases; and basic immunobiology. More information about this facility can be found at <http://www.niaid.nih.gov/reposit/tetramer/index.html>. The National Cancer Institute also provides funding for the Tetramer Facility.

The Division of Intramural Research (DIR) has a substantial intramural program that integrates genomics and combinatorial chemistry to speed development of new antibiotics for the control of TB. After contributing to the determination of the genomic sequence of *M.tb*, DIR investigators are now focusing on unraveling the functions of its various genes. This knowledge is critical to new drug and vaccine development and to understanding the molecular mechanisms involved in disease pathogenesis and the emergence of drug resistance. For example, despite the apparent lack of significant genetic differences among *M.tb* strains, there is mounting evidence that considerable variation exists in *M.tb* molecules that are important in disease pathogenesis. These differences may allow some

M.tb organisms to modify the host cellular immune response and thereby contribute to the observed diversity of tuberculosis disease. NIAID intramural scientists identified and described the functional relevance of a molecule—a phenolic glycolipid (PGL)—produced by a subset of *M.tb* organisms that shows “hyperlethality” in murine disease models. Disruption of PGL synthesis resulted in loss of hyperlethality and correlated with an increase in the release of substances that help the immune system fight *M.tb* infection. These findings demonstrate that the spectrum of TB disease observed in humans is likely to reflect not only variable host factors, but also the variable expression of bacterial factors, including PGL.

DIR scientists also are working on a number of different approaches to improve current TB drug therapies and to develop new drugs. This work will be facilitated by their development of the first comprehensive tool for the elucidation of the molecular mechanism of action of anti-tubercular drugs. Using DNA microarrays, the scientists characterized the *M.tb* genes that were transcribed or “turned on” in response to all known anti-TB drugs—thus revealing a molecular signature for each drug type that could be used to find new compounds with a similar signature. They also found that the transcriptional profile generated by a crude marine natural product predicted the mode of action of the pure active component. This tool will allow researchers to gain an immediate appreciation of the mechanism of an unknown agent and will greatly facilitate the drug discovery process.

DIR scientists also are continuing a project with colleagues from GlaxoSmithKline and St. Jude’s Children’s Hospital to develop an improved anti-tubercular drug based on thiolactomycin, a compound isolated from a soil bacterium. DIR collaborators at St. Jude’s used X-ray crystallography to determine the structure of thiolactomycin bound to its enzyme target. Using this structure as a guide, scientists are now synthesizing and testing derivatives of thiolactomycin that might be more active against

TB than thiolactomycin itself. This partnership is a model for the development of drugs against diseases that lack the financial impact necessary to attract independent attention from the global pharmaceutical industry. DIR scientists also have partnerships with colleagues from South Korea, Cambodia, and Nigeria to collaborate in studies of multidrug resistance and TB-HIV co-infection. In South Korea, an institutional review board (IRB) has been formed, a TB natural history clinical research protocol is in the final

stages of IRB approval, and clinical research training of staff has been completed.

NIAID support for TB research has led to significant advances in our understanding of the basic biology, microbiology, and immunology of TB, which will result in the development of new diagnostic tools, vaccine candidates, and therapeutic strategies to prevent and ultimately cure this devastating disease.

VACCINE RESEARCH AND DEVELOPMENT

Vaccines are perhaps the most powerful tool available to safeguard public health. Since a vaccine to prevent smallpox was invented in the 18th century, vaccines have been a safe, effective, and efficient means of preventing infectious diseases and have saved countless lives. In recent years, new technologies and new insights into the human immune system have greatly accelerated progress in vaccine research and have created exciting new opportunities to combat a wide spectrum of infectious diseases.

Because the potential to alleviate human suffering by developing new and more potent vaccines is so great, vaccine research is a top priority for Federal biomedical research. Within the Department of Health and Human Services, NIAID has the central role in vaccine research and development. The Institute's broad research programs on all classes of infectious diseases and the organisms that cause them, together with basic research on the immune system, catalyze its comprehensive efforts to create new and more effective vaccines. Many of these vaccine development activities are carried out in collaboration with scientists in government, industry, and at academic institutions. To set priorities for vaccine development, NIAID weighs the severity of a disease and the health benefits a vaccine might generate, and considers the scientific and programmatic opportunities, given the status of scientific knowledge.

The Division of Acquired Immunodeficiency Syndrome (DAIDS) supports the discovery and development of safe and effective vaccines to prevent HIV infection and AIDS worldwide. To reach this goal, DAIDS invests in a comprehensive portfolio of research grants and programs spanning basic vaccine research and preclinical testing of candidate HIV vaccines, through human clinical testing in the United States and internationally.

The Division of Microbiology and Infectious Diseases (DMID) supports a full spectrum of vaccine research to (1) prevent infectious diseases such as tuberculosis (TB), malaria, cytomegalovirus (CMV), group B streptococcus, and chlamydia infection; (2) serve fragile populations such as infants, older people, and immunocompromised people; (3) evaluate novel vaccine approaches such as oral, transcutaneous, and combination vaccines; and (4) improve existing vaccines.

Both DAIDS and DMID support large clinical networks and have vaccine production contracts that provide opportunities to move vaccine concepts into the early stages of clinical evaluation. Infrastructure for regulatory oversight, clinical site monitoring, and data management round out the vaccine development process. In collaboration with the Fogarty International Center, both Divisions support building infrastructure and training for clinical research in the United States and internationally.

The Division of Allergy, Immunology, and Transplantation (DAIT) supports research designed to apply the fundamental principles of immunology to the development of improved vaccines. The Division of Intramural Research (DIR) conducts a wide-ranging vaccine program. Extensive efforts are under way to develop vaccines to prevent diseases with global reach, such as malaria, AIDS, childhood respiratory infections, chlamydia, hepatitis C and E, West Nile, dengue, rabies, and genital herpes. NIAID's Dale and Betty Bumpers Vaccine Research Center (VRC) conducts research that facilitates the development of effective vaccines for human disease, with the primary focus of research being the development of vaccines for AIDS.

Division of Acquired Immunodeficiency Syndrome

The development of a safe and effective vaccine against HIV is critical to worldwide efforts to control the epidemic, and is one of NIAID's

highest priorities. DAIDS supports exploratory, high-risk, investigator-initiated HIV vaccine research at the earliest stages through the Innovation Grants Program for AIDS Vaccine Research. Other basic vaccine design and development efforts, including testing in animal models, mechanism-of-action studies, and studies of what human immune responses might correlate with protection against HIV are supported through the HIV Vaccine Research and Design Program. The Integrated Preclinical/Clinical AIDS Vaccine Development Program (IPCAVD) is a multi-project program that supports iterative product development and later stage vaccine optimization. Two IPCAVD grantees entered vaccines into human clinical trials in 2004.

To help expedite the development of promising HIV/AIDS vaccines, DAIDS also manages several novel public-private partnerships under a program titled HIV Vaccine Design and Development Teams (HVDDT). These contracts support consortia of scientists from industry and/or academia who have product development experience and who have invented promising vaccine concepts that are ready for accelerated product development. This program uses milestone-driven contracts as a way to encourage more rapid advancement of these vaccine candidates into clinical studies. Nine such contracts have been awarded since 2000. All are moving candidates rapidly through production and preclinical testing. Each of the original four contractors has developed experimental HIV vaccines that have entered human clinical trials. In 2003, three new HVDDT contracts were awarded to Alphavax, Inc., which makes alphavirus replicon-based vaccines; Epimmune, Inc., which makes multi-epitope DNA and modified vaccinia Ankara (MVA)-vectored vaccines; and Progenics Pharmaceuticals, Inc., which makes vaccines based on proteins from the HIV outer envelope.

The majority of NIAID-supported clinical HIV vaccine research is carried out through the HIV Vaccine Trials Network (HVTN). Now in its

fifth year, HVTN is a global network of clinical sites designed to address the scientific and public health needs of HIV vaccine and clinical research. HVTN conducts all phases of clinical trials to determine the safety, immunogenicity, and efficacy of candidate preventive HIV vaccines. The network's global capacity allows for rapid expansion as vaccine candidates enter the pipeline for testing and development, and for carrying out large-scale studies of the most promising preparations. The participation of international sites and the involvement of diverse populations through partnership with host country researchers, governments, and communities are critical components of NIAID's HIV vaccine effort. They allow for studies that examine differences resulting from HIV diversity, human genetic variations, nutritional status, the effects of other infections, and differences in access to healthcare—all of which may prove crucial to developing an effective vaccine that can be used around the world. In particular, the international capacity of the network facilitates studies of various HIV subtypes that may affect only a minority of the population, but may be important to the development of a vaccine that will protect people from different circulating strains of the virus.

During the past year, HVTN has initiated or continued several HIV vaccine studies. One candidate under investigation, in trial HVTN 040, is a novel noninfectious Alphavirus replicon HIV-1 subtype C vaccine designated AVX101 and made by Alphavax, Inc. The trial, which is being conducted at sites in the United States and South Africa, is the only one of its kind currently testing this kind of vaccine, which is based on a weakened Venezuelan equine encephalitis virus engineered to contain the HIV *gag* gene.

The first preventive HIV vaccine trial conducted at multiple international sites, HIVNET 026, has been successfully completed. This study evaluated the immunogenicity and safety of a canarypox virus engineered to express HIV proteins (ALVAC-HIV vCP1452) alone and

in combination with a recombinant form of the HIV coat protein (MN RGP120). It enrolled 160 participants; 40 each from Haiti, Trinidad, Brazil, and Peru. Preliminary data from the study confirmed the safety of the approach and provided additional information on the immunogenicity of this vaccine combination.

Collaboration and Partnerships

The AIDS Vaccine Research Working Group (AVRWG) assists NIH in developing a comprehensive research program to expedite the discovery and development of an HIV/AIDS vaccine. The members of the group provide technical assistance to NIH to help assess scientific opportunities, gaps in knowledge, and future directions of HIV vaccine research. As a working group of the NIAID AIDS Research Advisory Committee, the AVRWG makes recommendations to the Directors of NIAID and DAIDS concerning key scientific questions in vaccine development, including new vaccine designs, the mechanisms of protection in animal models, and potential new targets for vaccines.

A formal collaboration for HIV vaccine research, development, and testing between NIAID and the U.S. Army Medical Research and Materiel Command (USAMRMC) was established in 2003 through an interagency agreement with the Department of Defense (DoD). This collaboration helps to ensure that U.S. Government HIV vaccine research is well coordinated, efficient, and comprehensive. The collaboration gives NIAID greater access to the USAMRMC HIV/AIDS research program focused on vaccine product development and to DoD's extraordinary medical infrastructure, as well as to its extensive experience in establishing and supporting operations in underdeveloped regions.

Two vaccine trials have been initiated as part of this collaboration. The first is a phase III study, RV144, which began in Thailand in September 2003. This trial will evaluate an HIV vaccine

strategy known as "prime-boost," a combination of two different vaccines. One component is an engineered virus, ALVAC-HIV, while the other, AIDSVAX B/E, is based on purified HIV coat protein. These vaccines are designed to work together to activate both the cellular and antibody-producing arms of the immune system. The second study, RV151 is a placebo-controlled trial to evaluate three escalating doses of a novel candidate vaccine (LFn-p24), designed to induce strong and persistent cellular immune responses to HIV.

NIAID has led the development of the Partners in AIDS Vaccine Evaluation (PAVE) program, which plans and harmonizes clinical trials conducted by the Federal Government. Members include DAIDS, VRC, HVTN, the Centers for Disease Control and Prevention, and the U.S. Military HIV Research Program of the Department of Defense. PAVE is part of a global effort to share information and to increase operational efficiencies in HIV vaccine research and development. PAVE members also expect that working collaboratively to evaluate HIV/AIDS vaccines will foster scientific achievements that a single organization or institution would not be likely to accomplish on its own.

In the past year, the Gates Foundation and NIAID have sponsored a series of meetings to develop a strategic plan for the Global HIV Vaccine Enterprise. The Enterprise is a voluntary consortium of independent organizations committed to accelerating the development of a preventive vaccine for HIV/AIDS. At a recent meeting of G-8 leaders, President Bush announced that the U.S. Government would support the areas of research identified in the Enterprise strategic plan. NIAID has solicited applications for the creation of a Center for HIV/AIDS Vaccine Immunology (CHAVI) to be funded in FY 2005. CHAVI will support an intensive, multi-resourced, coordinated, consortium approach to address key scientific roadblocks in the creation of a safe and effective HIV vaccine for worldwide use. The goal is to

establish a highly collaborative, cooperative and interactive team of leading researchers who will devote the majority of their time to the application of state-of-the-art immunological tools toward this end.

Future Plans

DAIDS is moving to restructure its clinical research program by re-competing all of the current research networks, including HVTN, in 2006. The reorganization process is designed to develop a more efficient and highly collaborative clinical trials network that will enable DAIDS and its partners to meet future research challenges. DAIDS staff will continue to work with HVTN to expand the capabilities and capacity of existing international sites and to develop new sites. Extensive plans are underway to conduct multiple phase II trials of vaccine candidates in multisite studies that include both U.S. and international units; the preparations will focus on infrastructure development, technology transfer, and training.

In collaboration with Merck, Inc., the HVTN is currently conducting a “proof of concept” phase IIb HIV vaccine trial to evaluate the efficacy of a candidate called MRKAd5 HIV-1 gag/pol/nef, an adenovirus-based vaccine designed to prevent infection or delay HIV disease in 1,500 high-risk volunteers. The study will be conducted in the United States, the Caribbean, and South America.

A new Vaccine Developmental Resources Group (VDRG), consisting of internal NIAID staff and external scientists, will be established in 2005. This group will assist DAIDS staff in designing and reviewing protocols for the Simian Vaccine Evaluation Units, which carry out preclinical evaluation of vaccine candidates in nonhuman primates. VDRG will also assist NIAID in assessing the need for government support to advance promising candidate vaccines into and through clinical testing. NIAID will also continue to work within the Global HIV Vaccine

Enterprise to help ensure that the Enterprise scientific plan is implemented and will help to update the plan as needed.

Division of Microbiology and Infectious Diseases

Research leading to new and improved vaccines has long been a high priority for DMID. The goal of the DMID Program for the Accelerated Development of Vaccines, established in 1981, is to support research leading to vaccines that will improve health. DMID sets its priorities for vaccine research on the basis of the morbidity and mortality associated with each infectious disease, critical evaluation by the Institute of Medicine (IOM) of the National Academy of Sciences, assessment of research gaps and opportunities, and recommendations made by the National Vaccine Advisory Committee and other advisory groups.

DMID designs and implements a comprehensive research program to develop new or improved vaccines. Advances in microbiology, immunology, biotechnology, and other fields are applied to the development of new vaccines and to the improvement of existing vaccines, including:

- New vaccines against major diseases caused by respiratory syncytial virus (RSV); malaria; group A and group B streptococci; and other bacterial, parasitic, and fungal infections of both children and adults;
- Improved vaccines against diseases such as influenza virus, viral hepatitis, and TB;
- Vaccines to prevent neonatal infections such as group B streptococcus, and congenital diseases caused by CMV infection, toxoplasmosis, syphilis, gonorrhea, and chlamydia infections;
- New vaccines to prevent and control emerging diseases, including *Helicobacter pylori*, West Nile virus, severe acute

respiratory syndrome (SARS), and drug-resistant bacteria such as pneumococcus; and

- Novel technologies that enhance vaccine effectiveness, such as adjuvants, proteosomes, and plasmid DNA approaches.

Vaccine development is a long process, and is often done in collaboration with researchers in the pharmaceutical industry and academic laboratories. Vaccines are first screened for potential safety and efficacy in preclinical studies, including experiments using cell cultures and animal models. If the candidate vaccine looks promising, it may be evaluated in human clinical studies through the DMID Vaccine Evaluation Network, which includes the Vaccine and Treatment Evaluation Units and other units at universities across the United States. An integral part of NIAID vaccine research efforts, these vaccine units support carefully planned human clinical trials of novel bacterial, parasitic, and viral vaccines and other biologics in people of all ages and risk categories. DMID also supports research to develop new vaccine approaches that:

- Generate long-lasting protective immunity to various infectious agents;
- Favor the development of mucosal immunity or the production of a specific antibody;
- Increase the immunogenicity of candidate vaccines or favor the expression of a cell-mediated cytotoxic immune response; and
- Simplify immunization regimens to reduce the number of immunizations required for protection.

In addition, DMID supports vaccine research for emerging infectious diseases, including avian influenza and SARS.

DMID is internationally recognized as an effective participant in vaccine research and development issues with both U.S. and global impact. In the United States, DMID collaborates

with other federal agencies, including CDC and the Food and Drug Administration, on issues of vaccine research, vaccine safety, and national immunization strategies; this collaboration is coordinated through the National Vaccine Program Office (NVPO). Internationally, DMID participates with other national research agencies in the development and support of programs such as the Global Alliance for Vaccines and Immunization and the Multilateral Initiative on Malaria. DMID, together with the World Health Organization (WHO), U.S. Agency for International Development (USAID), Children's Vaccine Program at the Program for Appropriate Technology in Health, Wyeth Vaccines, and the London-based Medical Research Council, currently supports a randomized, controlled phase III efficacy trial in The Gambia, West Africa, to evaluate a pneumococcal conjugate vaccine manufactured by Wyeth containing nine separate antigens; the trial is designed to determine the impact of the vaccine on childhood pneumonia, which is a major cause of mortality in children under 5 years of age in this region.

The evaluation of vaccine safety is an integral component of the DMID vaccine research program. Safety is evaluated in every vaccine clinical trial sponsored by DMID; all participants are monitored closely for any adverse effects of the vaccinations they receive. Specific safety issues such as the use of novel cell substrates for vaccine manufacture and the evaluation of combination vaccines are explored through scientific consultation with other Federal agencies and in coordination with NVPO.

DMID also funds research to better understand safety of the vaccine preservative thimerosal. Since the 1930s, thimerosal has been added to some vaccines and other products because it kills bacteria and prevents bacterial contamination, particularly in multidose containers. When thimerosal is degraded or metabolized, one product is ethyl mercury, an organic derivative of mercury. Little is known about the effects of thimerosal exposure on humans and how it

compares to methyl mercury exposure, another organic mercury derivative. To learn more, DMID has initiated several research activities aimed at better understanding what happens to thimerosal once it is introduced into the body and how this compares to current knowledge of the pathway that metabolizes methyl mercury. DMID supported initial studies at the University of Rochester and continues follow-up studies in Argentina to measure mercury in blood and other samples from infants who received routine immunizations with thimerosal-containing vaccines. In addition, DMID and the National Institute of Environmental Health Sciences are cosponsoring a study in infant macaques to examine the pharmacokinetics and tissue distribution of thimerosal (given by injection) or methyl mercury (given orally). This study will address whether the exposure levels established as safe for methyl mercury are also appropriate for exposure limits on ethyl mercury.

In order to address concerns regarding specific vaccine safety issues, NIAID and CDC requested that the IOM establish an independent expert committee to review hypotheses regarding possible relationships between specific vaccines and adverse events. In response, IOM created the Immunization Safety Review Committee in September 2000. This committee reviews the state of knowledge about various specific immunization safety concerns and communicates its findings to healthcare providers and the public. In the past 3 years, the committee has met to review several important vaccine safety issues, including measles-mumps-rubella vaccine and autism, thimerosal-containing vaccines and neurodevelopmental disorders, multiple immunizations and immune dysfunction, hepatitis vaccine and neurological disorders, SV40 contamination of polio vaccine and cancer, the potential role of vaccinations in sudden unexpected death in infancy, and influenza vaccine and possible neurologic complications. Within several months of each meeting, the committee publishes reports of its findings and

makes recommendations about any additional actions that might be indicated.

DMID will continue to apply the latest advances in the fields of immunology, microbiology, and biotechnology to the development of new or improved vaccines against infectious diseases. Some recent applications of new technologies to vaccines include:

- Use of recombinant DNA technology for the production of defined immunogens as well as the preparation of plasmid DNA vaccines;
- Development and use of various immunomodulators to augment the immune response to poorly immunogenic candidate vaccines;
- Development of novel vaccine delivery systems to promote long-lasting immunity or to generate an immune response in a specific host tissues; and
- Research on novel approaches to the development of multicomponent vaccines and simpler vaccination regimens to reduce healthcare costs and the number of visits to healthcare facilities.

Division of Allergy, Immunology, and Transplantation

DAIT supports research on immunologic mechanisms and novel technologies applicable to vaccine design and development. The Division funds vaccine-related research projects on innate and adaptive immunity that aim to increase our ability to manipulate immune responses through better understanding of the underlying molecular, cellular, and systemic aspects of natural host defenses and antigen-specific immunity. Basic research topics that sustain vaccine development include innate immune receptors for pathogen molecules, antigen processing and presentation, the development of antibody and cellular immune responses, and the elaboration of immunologic memory. Topics more immediate to vaccine

applications include the development of new adjuvants to enhance immunity, the design of approaches that can induce protection in mucosal tissues, and the discovery of new ways to more effectively deliver immunizing agents. Other research that lays the groundwork for improved vaccines includes discovery of new pathogen epitopes—molecular structures of bacteria and viruses that stimulate immunity—and analyses of how variability in the human genome affects immune responses.

DAIT continues to fund four Vaccine Immunology Basic Research Centers that focus on the fundamental aspects of human protective immune mechanisms in infectious diseases. In addition, DAIT's Human Immunology Centers of Excellence Program supports many mechanistic studies that will contribute to our basic understanding of human immunity and vaccine responses.

In FY 2002, the Hyperaccelerated Award/Mechanisms in Immunomodulation Trials research program was expanded to support in-depth study of immunologic mechanisms during clinical trials of vaccines, including analyses of the underlying mechanisms of protective immunity, specificity and kinetics of immune responses, and immunologic memory. Studies proposed under this program must make use of clinical samples from a clinical trial supported by other funding. For example, NIAID recently funded research to analyze the cell-mediated immune responses of participants in a smallpox vaccine clinical trial.

DAIT has established a program called Application of Data on Human Leukocyte Antigen (HLA) to the Improvement of Vaccines, which supports several research projects on hepatitis C, tuberculosis, malaria, and HIV. For example, investigators funded through this program recently made a large step toward an effective malaria vaccine when they managed to predict which fragments of various malaria parasite proteins would bind to most members of a class of immune system receptor molecules

called the major histocompatibility complex (MHC); only these malaria protein fragments, called supertype antigenic epitopes, can activate the immune system to fight the parasite. The investigators also used proteomic and genomic techniques to select 27 genes expressed in different life stages of the malaria parasite candidates upon which to base a new malaria vaccine. They found that 16 of these 27 candidate genes contained supertype epitopes that were recognized by T cells from individuals vaccinated against malaria, but not by T cells from control individuals. Furthermore, some of these novel antigens stimulated the immune system more vigorously than any of the antigens that are the basis of experimental vaccines previously in clinical trials.⁶⁷ This approach will be invaluable in the discovery of vaccine candidates for other diseases as well.

Also under this program, DAIT supports the HLA Ligand/Motif Online Database, a Web-based, searchable database of human MHC molecules and the protein fragments that bind them. The database specifies the amino acid sequences of peptides derived from viral, bacterial, parasite, and human proteins in association with human MHC molecules. This resource enables users to search for specific human MHC/peptide combinations or to identify specific amino acid sequences that bind MHC molecules. The database is funded through a contract with the University of Oklahoma; further information is available at hlaligand.ouhsc.edu.

Grants funded under the Cooperative Centers for Translational Research on Human Immunology and Biodefense Program will facilitate the translation of research results from animal models such as the mouse into studies in humans. This program will develop new technologies to study human immune responses and regulation, and will fund research on human immune responses to NIAID Biodefense Category A, B, and C priority pathogens.

Contracts awarded under the Innate Immune Receptors and Adjuvant Discovery Program will support research on new adjuvants—additives that help stimulate human innate immune responses—from initial evaluation through preclinical testing. The adjuvant products developed under this program might be used both as vaccine adjuvants—to elicit T and B cell responses when co-administered with an immunogen—and as stand-alone immunomodulators—to stimulate short-term protective responses against many different infectious agents.

The Large-Scale Antibody and T Cell Epitope Discovery Program supports the rapid identification and verification of the specific molecular structures on pathogens, called epitopes, that antibodies or T cells recognize during the immune response. A related effort will establish a comprehensive centralized database to provide a Web-based, searchable source of information on pathogen epitopes for researchers. Included in the database is an analysis resource to facilitate data analysis and prediction of novel pathogen epitopes.

The NIAID Tetramer Facility produces MHC/peptide reagents that help detect T cells with different response characteristics; this program, which is also funded in part by the National Cancer Institute, has so far provided more than 1,900 tetramers to investigators worldwide. Reagents are provided for the study of T cell responses relevant to vaccine research and development for many diseases including intracellular bacterial, viral, and parasite infections and autoimmune diseases. Information on the NIAID Tetramer Facility can be found at www.niaid.nih.gov/reposit/tetramer/index.html.

Division of Intramural Research

DIR is working to develop vaccines against many infectious agents. This work often involves collaborative research and development efforts that span years—or decades—before coming to

fruition. For example, FluMist, the intranasal influenza vaccine, is the result of more than 20 years of collaborative research involving Dr. John Maassab of the University of Michigan School of Public Health and DIR scientists, with support from DMID. In addition, DIR has a long-term collaboration with scientists at the Johns Hopkins University to develop and test experimental vaccines against pandemic influenza, parainfluenza, respiratory syncytial virus (RSV), and the RSV-like human metapneumoviruses. DIR scientists also are working collaboratively to develop vaccines against SARS, multiple hepatitis viruses, rotavirus, and several members of the flavivirus family, including West Nile virus, St. Louis encephalitis, and dengue.

Dengue, for example, is a mosquito-borne virus that causes an estimated 50 to 100 million cases of dengue fever and several hundred thousand cases of potentially fatal dengue hemorrhagic fever each year. Four subtypes of dengue virus exist; infection with one subtype does not provide immunity to the others, so persons living in dengue-endemic areas can be infected by each subtype during their lifetimes. DIR scientists are developing a recombinant live-attenuated dengue virus vaccine that would provide protection against all four dengue subtypes. Components of this vaccine are currently undergoing phase I and II clinical testing.

DIR scientists are also working on a several other vaccines. The West Nile virus vaccine developed by DIR scientists will begin phase I clinical testing in 2005. In a collaborative effort with scientists from the military and industry, a hepatitis E vaccine developed by DIR researchers is undergoing clinical trial in an area where the disease is endemic. This work has recently been enhanced by the development of an ELISA test that measures neutralizing antibodies to hepatitis E virus, which will allow faster evaluation of the results of vaccine trials.

The Malaria Vaccine Development Branch (MVDB) is a large DIR program that maintains

collaborations with researchers in the United States and throughout the world; it also works closely with a variety of funding agencies, including the USAID and the Malaria Vaccine Initiative sponsored by the Bill and Melinda Gates Foundation. The MVBD is now preparing several malaria vaccine candidates for clinical testing. One of these is based on the *Plasmodium falciparum* antigen AMA1; see the malaria section on page 100 for more information.

Traditionally, identification of potential new vaccine candidates has been a slow and laborious process, with testing carried out one gene or protein at a time. Now, however, genome sequencing and other high-throughput analytic techniques provide far more rapid methods to identify the parts of an infectious agent that might form the basis of human vaccines. DIR scientists are using these modern tools to identify potential vaccine components for group A streptococcus, *Mycobacterium tuberculosis*, and other agents that cause significant morbidity and mortality worldwide.

Vaccine Research Center

The role of VRC is to stimulate multidisciplinary vaccine research and to translate basic research into candidate vaccines ready for clinical trials. After September 11, 2001, the biodefense role of VRC expanded to include development of preventive and therapeutic vaccines for potential agents of bioterrorism.

The VRC is very involved in the search for an HIV vaccine. In November 2002, the VRC launched a phase I clinical study of a novel DNA vaccine directed at the three most globally important HIV subtypes, or clades. The vaccine, developed by the VRC, incorporates HIV genetic material from clades A, B, and C, which together cause about 90 percent of all HIV infections around the world. This is the first multigene, multiclade HIV vaccine to enter human trials and marks an important milestone in the search for a single vaccine that targets U.S. subtypes of HIV

as well as clades causing the global epidemic. The first phase of the trial is being conducted by the VRC on the NIH campus and is designed to determine the vaccine's safety at three dose levels, and to evaluate how well the vaccine induces immune responses in 50 healthy, HIV-negative volunteers. Results from this trial are now being analyzed. A larger clinical trial to further evaluate safety, immune response, and schedule is being conducted through HVTN at several domestic sites, and a phase I clinical trial with 30 healthy volunteers will also be carried out in Uganda as a collaboration between the Makerere University-Walter Reed Project, DAIDS, and the VRC. The DAIDS Adult AIDS Clinical Trials Group is also conducting a phase I clinical trial of this vaccine in HIV-infected volunteers. Finally, the VRC has initiated a phase I clinical trial of a novel adenoviral HIV multiclade vaccine. The VRC eventually plans to combine DNA and adenoviral vector technologies into a prime-boost strategy for HIV vaccine development.

The Vaccine Research Center develops vaccines for biodefense. For example, the Center is currently testing an attenuated poxvirus called MVA as a safer alternative to the current smallpox vaccine. The vaccine was provided by Therion Biologics Corporation in collaboration with the VRC. Two phase I clinical trials are now under way testing MVA in both vaccinia-naïve and vaccinia-immune populations. In addition, VRC investigators, in collaboration with the U.S. Army Medical Research Institute for Infectious Diseases and the CDC, have developed a DNA vaccine to prevent Ebola virus infection; after promising results in nonhuman primates, a candidate Ebola vaccine began human testing in November 2003. In addition, the VRC is currently conducting preclinical testing of a fast-acting candidate Ebola vaccine that protects monkeys exposed to the virus 1 month after immunization; such a vaccine would be especially useful in an acute outbreak setting. If this vaccine proves similarly effective in humans, it could one day be used to quickly contain Ebola outbreaks

with ring vaccination—the same strategy used in the past against smallpox. A second generation product may also be evaluated that would potentially provide coverage for Marburg and possibly Lassa virus.

VRC also is developing vaccines for naturally emerging infections such as West Nile virus and SARS. For West Nile, VRC scientists have adapted an existing DNA plasmid vaccine platform to express West Nile proteins; these vaccine constructs are currently undergoing immunogenicity and viral challenge studies in rabbits. And in collaboration with Vical Inc., VRC has produced a supply of the vaccine to be used in a human phase I trial scheduled for early 2005.

In response to the recent global outbreak of SARS, VRC investigators began work immediately on the development of a potential vaccine. A Cooperative Research and Development Agreement and contract were established with GenVec, Inc., which is producing preclinical and clinical grade adenoviral vectors that express several SARS proteins. The VRC is evaluating these candidates preclinically, and will continue to develop and test adenovector-based vaccine candidates against SARS that are suitable for rapid advancement toward clinical trials. In addition, the VRC has contracted with Vical to manufacture a SARS DNA-based vaccine

encoding the spike (S) glycoprotein of the SARS coronavirus. Recent studies have demonstrated that this vaccine induces T cell and neutralizing antibody responses, as well as protective immunity, in a mouse model. A phase I trial of this recombinant DNA vaccine developed at the VRC is planned for early 2005.

The development of a contractor-leased and contractor-operated Vaccine Pilot Plant (VPP), which will manage production of multiple vaccine candidates originating from VRC, is a high priority. Working in concert with the Vaccine Production Laboratory located on the Bethesda, Maryland, campus, VPP will transfer new vaccine technology for pilot-scale production of vaccine material for use in clinical trials. With a projected completion date of late 2005, the VPP will have the capacity to produce four to eight clinical lots of vaccine annually.

Finally, an expanded capacity to conduct immunology assays is needed to support expanded NIAID-supported clinical trials of intramurally-generated vaccine products. To fill this need, the Immune Assessment Laboratory Service has been proposed to accelerate immunologic testing of candidate vaccines for HIV/AIDS, biodefense, and emerging or re-emerging infectious disease threats.

NIAID-SUPPORTED REPOSITORIES

NIAID's intramural and extramural researchers have developed an ample supply of resources and reagents that are used by scientists worldwide for basic research, applied research to develop therapeutics and vaccines, and commercialization. These resources include peptides, cell lines, monoclonal antibodies, viral vectors, and animal models.

Division of Acquired Immunodeficiency Syndrome (DAIDS)

NIH AIDS Research and Reference Reagent Program

The NIH AIDS Research and Reference Reagent Program acquires and distributes state-of-the-art reagents for AIDS-related research and makes these reagents available to qualified investigators throughout the world. It has grown significantly during the past 16 years and now has more than 5,200 reagents for public distribution. The AIDS Research and Reference Reagent Program also encourages and facilitates technology transfer through workshops, publication of methods, and provision of standardized panels and protocols; facilitates commercial development of reagents; and participates as an AIDS Collaborating Center of the World Health Organization (WHO).

The reagent program has immortalized and expanded white blood cells from more than 7,000 specimens from DAIDS-supported cohort studies of HIV-infected people, including the Multicenter AIDS Cohort Study, Women's Interagency HIV Study, and Women and Infants Transmission Study. These preserved cells will provide a source of DNA for future studies of genetic factors in HIV disease. By making these specimens available to the scientific community, DAIDS fosters collaboration among scientific investigators to promote further progress in the detection, treatment, and prevention of HIV

disease. More than 2,400 scientific publications have resulted, in part, from the use of reagents supplied by the NIH AIDS Reagent Program. To date, scientists from the United States and 65 foreign countries have been registered to receive reagents. In 2004 alone, more than 14,000 vials of reagents were distributed.

In 2003, the reagent program contract jump started the acquisition and distribution of urgently needed quality-controlled reagents for research on biodefense and emerging infectious disease agents such as anthrax and SARS.

Additional information is available at www.aidsreagent.org.

Vaccine Reagent Resource

Through the Vaccine Reagent Resource, DAIDS provides resources for the production or procurement of reagents essential for vaccine studies conducted by the HIV Vaccine Trials Network and the Simian Vaccine Evaluation Units, as well as other priority vaccine studies. These resources also provide for the quality assurance/control testing of reagents. Additional information is available at <http://www.niaid.nih.gov/daids/vaccine/reagentres.htm>.

Human HIV Specimens

Research on HIV transmission and disease progression patterns greatly benefits from a centralized system for receiving, cataloging, storing, and distributing samples collected from various well-characterized cohorts of HIV-infected individuals. NIAID provides state-of-the-art storage and computerized inventory management of specimens from domestic and international HIV epidemiology studies, HIV therapeutic and vaccine trials, and other prevention research studies through its central repositories.

Division of Allergy, Immunology, and Transplantation (DAIT)

Multiple Autoimmune Disease Genetics Consortium (MADGC)

Different autoimmune diseases are often found within a single family, suggesting common genetic contributions to the diseases. MADGC is a repository of genetic and clinical data and specimens from families in which two or more individuals are affected by two or more distinct autoimmune diseases. This repository provides well-characterized materials for use in research aimed at identifying the genes involved in autoimmune diseases. MADGC began enrolling families in May 2000. Additional information is available at www.madgc.org.

North American Rheumatoid Arthritis Consortium (NARAC)

NARAC is a collaborative registry and repository of information on families with rheumatoid arthritis. The NARAC database contains information on 902 families, encompassing 1,522 patient visits. Of the 902 families, data for more than half have been validated, including 600 affected sibling pairs. The family registry and the repository samples should facilitate the characterization of the genes underlying susceptibility to rheumatoid arthritis and are available to all investigators. More information can be found at www.naracdata.org. This registry is cosponsored by the National Institute of Arthritis and Musculoskeletal and Skin Diseases and the Arthritis Foundation.

Primary Immunodeficiency Diseases Registry (PIDR)

PIDR was established by NIAID to maintain clinical information on patients in the United States affected by primary immunodeficiency diseases. For each disease, the registry collects information on the natural course of the disease, including early and late complications, effects of therapy, and causes of death. The diseases included in the registry are chronic

granulomatous disease, hyper-IgM syndrome, severe combined immunodeficiency disease, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, common variable immunodeficiency, leukocyte-adhesion deficiency, and DiGeorge syndrome. Researchers may apply to the registry to request contact information for physicians who are caring for primary immunodeficiency disease patients. In 2003, a repository also was established. The repository will contain cell lines and DNA from patients with primary immunodeficiency diseases. Researchers may apply to the repository for access to this material. For PIDR-related information see http://www.primaryimmune.org/med_programs/pid_registry.htm.

National MHC Tetramer Core Facility

In FY 1998, NIAID established a contract facility to provide researchers with peptide-major histocompatibility complex (MHC) tetrameric molecules for analyzing antigen-specific T cell responses. Because T cells are central to virtually all immune responses, this technology is applicable to studies in many areas including basic immune mechanisms, infectious diseases, vaccination, autoimmunity, transplant rejection, and tumor therapy. By centralizing the production of these tetramers, individual, defined peptide-MHC molecules can be produced economically and can be made available to investigators at greatly reduced expense. The MHC tetramer core facility is located at Emory University in Atlanta, Georgia, under the direction of Dr. John Altman.

Division of Intramural Research (DIR)

Transgenic and Gene-Targeted Mice Repository

DIR, in collaboration with DAIT, supports facilities for the acquisition, breeding, and distribution of transgenic and gene-targeted (knockout) mice, which are mice that are genetically engineered to serve as animal models for human diseases that do not occur

in nonhuman species. The repository provides these mice to both intramural and extramural investigators through the NIAID/Taconic exchange programs for use in research and for development of clinical therapies in various infectious and immunologic diseases.

Division of Microbiology and Infectious Diseases (DMID)

Global Health

Malaria Research and Reference Reagent Repository (MR4)

The malaria repository was established to acquire, produce, and distribute malaria research reagents, reference materials, and other information to qualified investigators throughout the world. A major component of the program is the quality control of reagents, standardization of protocols, and exploration of new technologies. International workshops and training sessions will be organized to stimulate and support both laboratory-based and field-based research. The long-term goal of the repository program is to promote technology transfer as well as to facilitate research leading to commercial development of reagents for malaria diagnostics, prevention, and treatment. NIAID established the repository in support of the Multilateral Initiative on Malaria, a research capacity-strengthening program in partnership with other national and international organizations. Additional information is available at www.malaria.mr4.org.

Tuberculosis Research Materials and Vaccine Testing

Mycobacterium tuberculosis (*M.tb*), the organism responsible for tuberculosis (TB), is difficult and time-consuming to grow and, because it is transmitted via aerosols, should be studied only in appropriate biohazard facilities. DMID funds a repository to provide *M.tb*-derived materials to qualified TB investigators worldwide in basic and clinical research areas, allowing work to begin quickly and eliminating the need for

these investigators to have their own biohazard facilities. DMID also supports the screening of potential anti-TB vaccine candidates, which are provided by individual researchers, in established small-animal, low-dose, aerosol-challenge models. Additional information is available at www.cvmb.colostate.edu/microbiology/tb/top.htm.

Leprosy Research Support and Armadillo Colony

Despite the availability of multidrug regimens to cure leprosy, leprosy has remained a problem worldwide. A major obstacle in leprosy research is the fact that *Mycobacterium leprae*, the organism responsible for leprosy, cannot be cultured in laboratory media and therefore has to be propagated in animals. To help alleviate this problem, DMID supports the maintenance of an armadillo colony, one of the best animal model systems of *M. leprae* infection and disease. DMID also funds a repository of viable *M. leprae* and purified, defined reagents derived from *M. leprae*, which are available to researchers worldwide. Additional information is available at www.cvmb.colostate.edu/mip/leprosy/index.html.

Schistosomiasis and Filariasis Research Repositories

For more than 30 years, NIAID contracts have supported two helminth resources that serve the research community. The Schistosome Resource Center (www.schisto-resource.org) is maintained by the Biomedical Research Institute (Dr. Fred Lewis, Principal Investigator), and the Filaria Resource Center is maintained by the University of Georgia (Dr. John McCall, Principal Investigator). Investigators worldwide can obtain schistosome or filaria life stages for research or teaching purposes. Selected materials, including molecular and genomic reagents, are made available to biochemists, immunologists, vector biologists, and others who cannot reasonably maintain their own life cycles due to lack of space, time, funding, or requisite expertise. Investigators can obtain parasites, vectors, and mammalian hosts free of charge, excluding shipping costs. In

addition to fostering schistosomiasis and filarial research, these two NIAID resources serve as valuable backup facilities for investigators who have experienced problems with their own established life cycles.

Pneumococcal Reference Laboratory

This laboratory provides reference and resource services and expertise to facilitate the evaluation of improved pneumococcal vaccines and other bacterial respiratory pathogens. A major objective is to establish a consensus assay and to improve and modify procedures for measuring antibody activity to pneumococci. The laboratory also provides radiolabeled polyribosylribose phosphate (PRP) and/or suitably derivatized PRP and purified PRP to laboratories for the performance of *Haemophilus influenzae* type B assays and for calibration of immunodiagnostic assays.

Viral Infections

Repository for Biological Reagents and Reference Standards

This repository stores and distributes serological and microbiological reagents for use as reference standards and for research in infectious and immunologic diseases. As a WHO Collaborating Center for Antiviral Drugs and Interferon, this NIAID repository is responsible for the storage and worldwide distribution of WHO international interferon standards and reference reagents.

***In Vitro* Antiviral Screening Program**

NIAID maintains a screening program to provide *in vitro* screens for evaluation of potential antiviral agents for inhibitory activity against herpesviruses (herpes simplex viruses 1 and 2, varicella-zoster virus, Epstein-Barr virus, cytomegalovirus, human herpesvirus 6 and 8), orthopoxviruses (vaccinia and cowpox), respiratory viruses (influenza A, influenza B, parainfluenza, respiratory syncytial virus, measles, rhinoviruses, adenoviruses, and severe acute respiratory syndrome coronavirus), viral

hemorrhagic fevers and encephalitic viruses (Venezuelean equine encephalitis, Pichinde, Punta Toro, yellow fever, West Nile virus, and dengue fever), hepatitis B and C, BK virus, and papillomaviruses. These *in vitro* screens provide selective indexes of potential compounds, thus providing early information to guide selection and prioritization. Active compounds can then be evaluated against several virus strains and for assessment of pharmacologic properties.

World Reference Center for Emerging Viruses and Arboviruses

NIAID maintains the World Reference Center for Emerging Viruses and Arboviruses at the University of Texas Medical Branch at Galveston. The Center has reference virus sera and seed lots of various virus strains, which can be distributed to qualified researchers and facilities. Although focused primarily on arthropod-borne and rodent-borne viruses, other viral reagents are also available. This international program involves characterizing viruses transmitted to people and animals by mosquitoes and other arthropod vectors or animal hosts and researching the epidemiology of arboviruses and emerging viruses in the United States and in other countries. Center activities include (1) virus identification and characterization; (2) investigation and diagnosis of disease outbreaks; (3) preparation and distribution of certified virus stocks and reagents to qualified investigators/facilities; (4) development of new animal models of arboviral and other emerging diseases and studies of arboviral pathogenesis; (5) training of professional and technical personnel from any region of the world in arbovirus techniques; and (6) dissemination of information on arbovirus taxonomy, diagnostic techniques, and disease outbreaks. Because of the reference center's extensive virus reference collection, unique diagnostic capabilities, and contact with virologists and public health laboratories throughout the world, it plays an important role in the global surveillance network for emerging viral diseases.

Biodefense and Emerging Infectious Diseases

The Network on Antimicrobial Resistance in *Staphylococcus aureus* (NARSA)

NARSA is a multidisciplinary international network of basic scientists, clinical microbiologists, and clinical investigators that focuses on *S. aureus* and other staphylococcal species that exhibit antimicrobial resistance. NARSA is responsible for tracking and procuring staphylococcal isolates (including *S. aureus* and the coagulase-negative staphylococci) with reduced susceptibility to vancomycin (minimum inhibiting concentrations > 4 mg/ml) for inclusion in a central repository. A central repository of these isolates provides a standardized source of isolates for investigative studies. The strains collected for the NARSA repository are readily available to researchers. The well-characterized isolates collected and stored in the centralized NARSA repository, together with the registry database to which they are linked, provide the general scientific community with a valuable research resource for multidisciplinary investigation. Additional information is available at <http://www.narsa.net/content/default.jsp>.

In Vitro and Animal Models for Emerging Infectious Diseases and Biodefense

The *In Vitro* and Animal Models for Emerging Infectious Diseases and Biodefense Program provides a broad range of preclinical developmental resources for product development and clinical testing. The areas of this contract include *in vitro* screening for antimicrobial activity, clinical isolate panels for selected bacterial pathogens, small animal models, nonhuman primate models and studies, safety/toxicology and immunogenicity testing for vaccines, and safety/toxicology and pharmacology testing for therapeutics.

Biodefense and Emerging Infectious Diseases Research Resources Program

The Biodefense and Emerging Infectious Diseases Research Resource Program acquires, authenticates, stores, and distributes state-of-the-art research and reference reagents and standardized panels to the scientific community. This resource, funded in 2003, includes the capability to validate, expand, and produce biological agents including cell lines, clones, proteins, monoclonal and polyclonal antibodies, and diagnostic reagents and tools. The acquisition of NIAID Category A priority pathogens and reagents for research on these threat agents is a high priority.

Network for Large-Scale Sequencing of Microbial Genomes

NIAID has established a state-of-the-art, high-throughput DNA sequencing center that can rapidly sequence genomes of microbes and invertebrate vectors of infectious diseases. Data will be released in a timely, publicly accessible manner, with preliminary information about open reading frames and the annotation of gene function provided to the research community.

Pathogen Functional Genomics Resource Center (PFGRC)

PFGRC is a centralized facility that provides the research community with resources necessary to conduct functional genomics research on human pathogens and invertebrate vectors. PFGRC provides scientists with microarrays, genotyping, bioinformatics, and a repository for clone access and other reagents. In addition, PFGRC has the capability to train scientists in the latest techniques in functional genomics and development of emerging genomic technologies. Additional information is available at <http://pfgrc.tigr.org>.

REFERENCES

1. UNAIDS. AIDS epidemic update: December 2004. Available from: <http://www.unaids.org/wad2004/report.html>.
2. Dybul M et al. A proof-of-concept study of short-cycle intermittent antiretroviral therapy with a once-daily regimen of didanosine, lamivudine, and efavirenz for the treatment of chronic HIV infection. *J Infect Dis* 189:1974–1982 (2004).
3. Farel CE et al. Induction and maintenance therapy with intermittent interleukin-2 in HIV-1 infection. *Blood* 103:3282–3286 (2004).
4. Burke JP. Infection control—a problem for patient safety. *N Engl J Med* 348(7):651–656 (2003).
5. NIAID [Internet]. The Problem of Antibiotic Resistance, April 2004. Available from: <http://www.niaid.nih.gov/factsheets/antimicro.htm>.
6. Blot SI, Vandewoude KH, and Hoste EA. Outcome and attributable mortality in critically ill patients with bacteremia involving methicillin-susceptible and methicillin-resistant *Staphylococcus aureus*. *Arch Intern Med*. 162(19):2229–35 (2002); Cosgrove SE et al. Comparison of mortality associated with methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* bacteremia: a meta-analysis. *Clin Infect Dis*. 36(1):53–9 (2003); Carmeli Y et al. Health and economic outcomes of vancomycin-resistant enterococci. *Arch Intern Med*. 162(19):2223–8 (2002).
7. CDC Division of Bacterial and Mycotic Diseases [Internet]. Drug-resistant *Streptococcus pneumoniae* Disease, December 2003. Available from: http://www.cdc.gov/ncidod/dbmd/diseaseinfo/drugresisstreppneum_t.htm; World Health Organization [Internet]. Initiative for Vaccine Research, 2005. Available from: http://www.who.int/vaccine_research/documents/new_vaccines/en/index2.html.
8. NIAID [Internet]. Focus On Bug-Borne Disease Research: Malaria, June 29, 2004. Available from: <http://www2.niaid.nih.gov/Newsroom/FocusOn/BugBorne01/malaria.htm>.
9. World Health Organization [Internet]. Executive Summary, Third Global Report: WHO/IUATLD Global Project on Anti-Tuberculosis Drug Resistance Surveillance, 2004. Available from: www.who.int/gtb/publications/drugresistance/2004/index.htm.
10. Taylor DN. The growing problem of antimicrobial resistance among enteric pathogens. *Clin Updates Infect Dis*. 6:1–3 (2003).
11. Parry CM. Antimicrobial drug resistance in *Salmonella enterica*. *Curr Opin Infect Dis*. 16:467–472 (2003).
12. Tjaniadi P et al. Antimicrobial resistance of bacterial pathogens associated with diarrheal patients in Indonesia. *Am J Trop Med Hyg*. 68:666–670 (2003).
13. Boshoff HI et al. DnaE2 polymerase contributes to *in vivo* survival and the emergence of drug resistance in *Mycobacterium tuberculosis*. *Cell*. 113:183–193 (2003).
14. Vuong C et al. Polysaccharide intercellular adhesion (PIA) protects *Staphylococcus epidermidis* against major components of the human innate immune system. *Cell Microbiol*. 6(3):269–75 (2004).
15. AAAAI [Internet]. The Allergy Report: Science-Based Findings on the Diagnosis & Treatment of Allergic Disorders, December 2004. Available from: <http://www.niaid.nih.gov/factsheets/allergystat.htm>.
16. Matricardi PM et al. Hay fever and asthma in relation to markers of infection in the United States. *J Allergy Clin Immunol*. 110:381–387 (2002).
17. Sampson H. Peanut allergy. *N Engl J Med*. 346:1294–1299 (2002).
18. CDC, National Center for Health Statistics [Internet]. Asthma Prevalence, Health Care Use and Mortality, 2002. Available from: <http://www.cdc.gov/nchs/products/pubs/pubd/hestats/asthma/asthma.htm>.
19. Jarrett CO et al. Flea-borne transmission model to evaluate vaccine efficacy against naturally acquired bubonic plague. *Infect Immun*. 72:2052–2056 (2004).

20. Kobayashi SD et al. Bacterial pathogens modulate an apoptosis differentiation program in human neutrophils. *Proc Nat'l Acad Sci USA*. 100: 10948–10953 (2003).
21. Earl PL et al. Immunogenicity of a highly attenuated MVA smallpox vaccine and protection against monkeypox. *Nature*. 428:182–185 (2004).
22. Hoebe K et al. Identification of *Lps2* as a key transducer of MyD88-independent TIR signaling. *Nature*. 433:523–527 (2003).
23. Boshoff HI et al. The transcriptional responses of *Mycobacterium tuberculosis* to inhibitors of metabolism: novel insights into drug mechanisms of action. *J Biol Chem*. 279:40174–40184 (2004).
24. Mannon PJ et al. Anti-interleukin-12 antibody for active Crohn's disease. *New Eng J Med*. 351: 2069–2079 (2004).
25. Langford CA, Talar-Williams C, and Sneller MC. Mycophenolate mofetil for remission maintenance in the treatment of Wegener's granulomatosis. *Arthritis Rheum*. 51:278–283 (2004).
26. Mentink-Kane MM et al. IL-13 receptor alpha 2 down-modulates granulomatous inflammation and prolongs host survival in schistosomiasis. *Proc Nat'l Acad Sci USA*. 101:586–590 (2004).
27. Subbarao K et al. Prior infection and passive transfer of neutralizing antibody prevent replication of SARS coronavirus in the respiratory tract of mice. *J Virol*. 78:3572–3577 (2004).
28. Dye C et al. Consensus statement. Global burden of tuberculosis: estimated incidence, prevalence, and mortality by country. WHO Global Surveillance and Monitoring Project. *JAMA*. 282:677–686 (1999).
29. WHO [Internet]. Tuberculosis fact sheet No. 104, revised March 2004. Available from: <http://www.who.int/mediacentre/factsheets/fs104/en>.
30. Final 2003 reports of notifiable diseases. *MMWR* 53(30):687–706 (2004). Available from: <http://www.cdc.gov/mmwr/PDF/wk/mm5330.pdf>.
31. Notifiable diseases/deaths in selected cities weekly information. *MMWR*. 52(53):1291–1299 (2004). Available from: <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5253md.htm>.
32. Burgdorfer W. The enlarging spectrum of tick-borne spirochetoses: R.R. Parker Memorial Address. *Rev Infect Dis*. 8:932–940 (1986).
33. National Vital Statistics Report 50(16):13–36 (2002). Available from: http://www.cdc.gov/nchs/fastats/pdf/nvsr50_16t1.pdf.
34. WHO [Internet]. Cumulative number of confirmed cases of human influenza A(H5N1) since 28 January 2004. Available from: http://www.who.int/csr/disease/avian_influenza/country/cases_table_2004_10_04/en.
35. WHO [Internet]. Hepatitis C fact sheet No. 164, revised October 2000. Available from: <http://www.who.int/mediacentre/factsheets/fs164/en>.
36. CDC [Internet]. Viral Hepatitis C fact sheet, reviewed January 2005. Available from: www.cdc.gov/ncidod/diseases/hepatitis/c/fact.htm.
37. Ibid.
38. NIH [Internet]. National Institutes of Health Consensus Development Conference Statement, Management of Hepatitis C: 2002. June 10–12, 2002. Available from: http://consensus.nih.gov/cons/116/091202116cdc_statement.htm.
39. Bartosch B et al. *In vitro* assay for neutralizing antibody to hepatitis C virus: evidence for broadly conserved neutralization epitopes. *Proc Nat'l Acad Sci USA*. 100:14199–14204 (2003).
40. Sakai A et al. The p7 polypeptide of hepatitis C virus is critical for infectivity and contains functionally important genotype-specific sequences. *Proc Nat'l Acad Sci USA*. 100:11646–11651 (2003).
41. The World Bank Group [Internet]. Malaria at a glance fact sheet, updated October 2003. Available from: www1.worldbank.org/hnp/Malaria/Malaria_publications.asp.
42. Morgan WJ et al. Results of a home-based environmental intervention among urban children with asthma. *N Engl J Med*. 351(11):1068–1080 (2004).

43. NCCAM [Internet]. Hepatitis C and complementary and alternative medicine: 2003 update. Available from: <http://nccam.nih.gov/health/hepatitisc/index.htm>; NIH [Internet]. NIH consensus statement on management of hepatitis C: 2002. Available from: http://consensus.nih.gov/cons/116/hepatitis_c_consensus.pdf.
44. CDC [Internet]. Cases of HIV infection and AIDS in the United States. (HIV/AIDS surveillance report, 2003, Vol. 15) Available from: <http://www.cdc.gov/hiv/stats/2003SurveillanceReport.htm>.
45. WHO [Internet]. Number of women living with HIV increases in each region of the world, November 23, 2004. Available from: http://www.who.int/mediacentre/news/releases/2004/pr_unaids/en.
46. CDC [Internet]. Division of HIV/AIDS prevention. Basic statistics, December 20, 2004. Available from: <http://www.cdc.gov/hiv/stats.htm#aidsstats>.
47. NIAID [Internet]. HIV infection in infants and children, July 2004. Available from: <http://www.niaid.nih.gov/factsheets/hivchildren.htm>.
48. NIAID [Internet]. Strategic plan for addressing health disparities: fiscal years 2002–2006. Available from: http://www.niaid.nih.gov/healthdisparities/NIAID_HD_Plan_Final.pdf.
49. CDC [Internet]. STD surveillance 2003. Available from: <http://www.cdc.gov/std/stats/trends2003.htm>.
50. CDC [Internet]. STD Prevention—Chlamydia Fact Sheet, May 2004. Available from: <http://www.cdc.gov/std/Chlamydia/STDFact-Chlamydia.htm>.
51. CDC [Internet]. STD Prevention—Genital Herpes Fact Sheet, May 2004. Available from: <http://www.cdc.gov/std/Herpes/STDFact-Herpes.htm>.
52. CDC [Internet]. Cases of HIV infection and AIDS in the United States. (HIV/AIDS surveillance report, 2003, Vol. 15) Available from: <http://www.cdc.gov/hiv/stats/2003SurveillanceReport.htm>.
53. CDC [Internet]. STD Prevention—Syphilis Fact Sheet, May 2004. Available from: <http://www.cdc.gov/std/Syphilis/STDFact-Syphilis.htm>.
54. CDC [Internet]. STD Facts—Trichomoniasis Fact Sheet, May 2004. Available from: <http://www.cdc.gov/std/Trichomonas/STDFact-Trichomoniasis.htm>.
55. Kerman RH et al. Influence of race on crossmatch outcome and recipient eligibility for transplantation. *Transplantation*. 53:64–67 (1992); Norman DJ et al. Cadaveric kidney allocation in the United States: a critical analysis of the point system. *Transplant Proc*. 27:800 (1995).
56. Beatty PG, Mori M, and Milford E. Impact of racial genetic polymorphism on the probability of finding an HLA-matched donor. *Transplantation*. 60(8):778–783 (1995).
57. WHO [Internet]. Tuberculosis fact sheet No. 104, March 2004. Available from: <http://www.who.int/mediacentre/factsheets/fs104/en>; Global tuberculosis control—surveillance, planning, financing, 2004. Available from: http://www.who.int/tb/publications/global_report/en.
58. CDC [Internet]. Targeted tuberculin testing and treatment of latent tuberculosis infection. (see Table 2 – “Incidence of active tuberculosis (TB) in persons with a positive tuberculin test, by selected risk factors”). *MMWR* 49(RR06): 1–54 (June 9, 2000). Available from: <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4906a1.htm#tab2>.
59. CDC [Internet]. Trends in Tuberculosis—United States, 1998–2003. *MMWR* 53(10):209–214 (March 19, 2004). Available from: www.cdc.gov/mmwr/preview/mmwrhtml/mm5310a2.htm.
60. American Social Health Association [Internet]. Facts and Answers about STDs: STD Statistics. Research Triangle Park, NC; 2005. Available from: www.ashastd.org/stdfaq; CDC [Internet]. Tracking the Hidden Epidemics: Trends in STDs in the United States 2000. Available from: http://www.cdc.gov/nchstp/dstd/Stats_Trends/Trends2000.pdf.

61. Highleyman L. STDs Increase Risk for HIV [Internet]. San Francisco, CA: *Bulletin of Experimental Treatment for AIDS*, Autumn 2000. Available at: www.thebody.com/sfaf/autumn00/std.html#synergy.
62. The Organ Procurement and Transplantation Network [Internet]. Data. Available from: www.optn.org/data. Accessed October 4, 2004.
63. Ibid.
64. Ibid.
65. WHO [Internet]. Tuberculosis Fact Sheet No. 104, revised March 2004. Available from: <http://www.who.int/mediacentre/factsheets/fs104/en>; and Global tuberculosis control—surveillance, planning, financing, 2004. Available from: http://www.who.int/tb/publications/global_report/en.
66. NIAID [Internet]. Tuberculosis Antimicrobial Acquisition and Coordinating Facility: Global discovery program for novel anti-tuberculosis drugs, 2004. Available from: www.taacf.org.
67. Doolan DL et al. Identification of *Plasmodium falciparum* antigens analysis of genomic and proteomic data. *Proc Nat'l Acad Sci USA*. 100:9952–9957 (2003).

COUNCIL, REVIEW COMMITTEES, AND WORKING GROUP

NATIONAL ADVISORY ALLERGY AND INFECTIOUS DISEASES COUNCIL

Composed of both scientists and laypersons, the National Advisory Allergy and Infectious Diseases Council makes final recommendations on the scientific merit of NIAID-assigned applications for research grants, cooperative agreements, and research training awards. Council review is the final step in the NIH peer review process, and its recommendations are based both on scientific merit, as judged by the scientific review groups, and on the relevance of the proposed study to the Institute's programs and priorities. Applications reviewed relate to all activities within the NIAID research mission, including the fields of immunology, allergic and immunologic diseases, transplantation immunology, microbiology and infectious diseases, and AIDS and AIDS-related conditions. Through its subcommittees, the Council conducts concept clearances and advises NIAID on general policy.

The National Advisory Allergy and Infectious Diseases Council roster is located at the Web site www.niaid.nih.gov/facts/council.htm.

Roster

Anthony S. Fauci, M.D. (Chair)

Director

National Institute of Allergy and Infectious Diseases

National Institutes of Health
Bethesda, Maryland 20892

William Bertrand, Ph.D.

Executive Director

Payson Center for International Development
and Technology Transfer

Tulane University
New Orleans, Louisiana 70118
(Term expires October 31, 2004)

Stanley W. Chapman, M.D.

Professor of Medicine and Microbiology

Division of Infectious Diseases
University of Mississippi Medical Center
Jackson, Mississippi 39216-4505
(Term expires October 31, 2007)

Charlotte W. Collins, J.D.

Attorney

Powell, Goldstein, Frazier and Murphy
Washington, DC 20004
(Term expires October 31, 2004)

Anthony D'Alessandro, M.D.

Professor of Surgery

Department of Surgery
University of Wisconsin Hospital and Clinics
Madison, Wisconsin 53792
(Term expires October 31, 2007)

Charles E. Davis, M.D.

Assistant Professor of Medicine

Institute of Human Virology
School of Medicine
University of Maryland, Baltimore
Baltimore, Maryland 21201
(Term expires October 31, 2007)

Luiz Diaz, M.D.

Professor and Chairman

Department of Dermatology
University of North Carolina at Chapel Hill
Chapel Hill, North Carolina 27599
(Term expires October 31, 2005)

Jay Brooks Jackson, M.D.

Professor and Chairman of Pathology

Department of Pathology
Johns Hopkins Medical Institutions
Baltimore, Maryland 21287
(Term expires October 31, 2007)

Fred Jones, Jr., Ph.D.

Dean Emeritus

School of Graduate Studies and Research
Meharry Medical College
Nashville, Tennessee 37208
(Term expires October 31, 2004)

Dorothy E. Lewis, Ph.D.

Professor

Department of Immunology
Baylor College of Medicine
Houston, Texas 77030
(Term expires October 31, 2005)

Margaret A. Liu, M.D.

Vice Chairman, Transgene

Consultant, Bill and Melinda Gates Foundation
Lafayette, California 94549
(Term expires October 31, 2005)

Richard M. Locksley, M.D.

Chief

Division of Infectious Diseases
Department of Medicine
University of California, San Francisco
San Francisco, California 94143
(Term expires October 31, 2005)

Gerald L. Mandell, M.D.

Professor of Medicine

Owen R. Cheatham Professor of the Sciences
University of Virginia Health Sciences Center
Charlottesville, Virginia 22908
(Term expires October 31, 2004)

Anne Munoz-Furlong

Chief Executive Officer and Founder

Food Allergy and Anaphylaxis Network
Fairfax, Virginia 22030
(Term expires October 31, 2007)

Raymond C. O'Brien, J.D.

Professor of Law

Columbus School of Law
Catholic University of America
Washington, DC 20064
(Term expires October 31, 2007)

Anjana Rao, Ph.D.

Senior Investigator

Center for Blood Research
Harvard Medical School
Boston, Massachusetts 02115
(Term expires October 31, 2007)

Ruth M. Ruprecht, M.D., Ph.D.

Professor of Medicine

Dana-Farber Cancer Institute
Boston, Massachusetts 02115
(Term expires October 31, 2007)

Nathan Thielman, M.D., M.P.H.

Medical Director for Infectious Diseases/HIV Clinics

Division of Infectious Diseases
Duke University Medical Center
Durham, North Carolina 27710
(Term expires October 31, 2007)

Gail W. Wertz, Ph.D.

Professor

Department of Microbiology
University of Alabama at Birmingham
Birmingham, Alabama 35294-2170
(Term expires October 31, 2007)

Ex Officio Members

Lawrence R. Deyton, M.S.P.H., M.D.

Director, AIDS Service

U.S. Department of Veterans Affairs
Washington, DC 20420

James M. Hughes, M.D.

Director

National Center for Infectious Diseases
Centers for Disease Control and Prevention
Atlanta, Georgia 30333

Major General Lester Martinez-Lopez

Commanding General

U.S. Army Medical Research and Materiel
Command
Fort Detrick, Maryland 21702

Tommy G. Thompson

Secretary

Department of Health and Human Services
Washington, D.C. 20201

Elias A. Zerhouni, Jr., M.D.

Director

National Institutes of Health
Bethesda, Maryland 20802

Executive Secretary

John J. McGowan, Ph.D.

Director

Division of Extramural Activities
National Institute of Allergy and Infectious
Diseases
National Institutes of Health
Bethesda, Maryland 20892

ACQUIRED IMMUNODEFICIENCY SYNDROME RESEARCH REVIEW COMMITTEE

In its role within the NIH peer review system, the Acquired Immunodeficiency Syndrome (AIDS) Research Review Committee advises the Directors of the NIH and NIAID with respect to programs and activities related to AIDS and the prevention and treatment of the major opportunistic infections associated with AIDS. The Committee provides a primary review of selected grant applications, cooperative agreements, and contract proposals for special research and training programs. These include program projects and centers, institutional National Research Service Awards, conference grants, and special developmental award programs in AIDS-related areas. The Committee recommends ratings for applications and proposals that it determines to have significant and substantial scientific merit and advises the Institute Director on the development of new programs in the above-mentioned scientific areas.

The AIDS Research Review Committee roster is located at the Web site www.niaid.nih.gov/facts/revcom.htm.

Roster

Stephen Dewhurst, Ph.D. (Chair)

Professor

Department of Microbiology and Immunology
School of Medicine and Dentistry
University of Rochester
Rochester, New York 14642
(Term expires June 30, 2004)

Arlene D. Bardeguet, M.D.

Associate Professor

Department of Obstetrics and Gynecology
University of Medicine and Dentistry
New Jersey Medical School
Newark, New Jersey 07103
(Term expires June 30, 2004)

Yvonne J. Bryson, M.D.

Professor and Chief

Division of Infectious Diseases
School of Medicine
University of California, Los Angeles
Los Angeles, California 90095
(Term expires June 30, 2005)

Farley R. Cleghorn, M.B.B.S.

Assistant Professor

Department of Medicine and Epidemiology
Institute of Human Virology
University of Maryland
Baltimore, Maryland 21201
(Term expires June 30, 2005)

Robert W. Doms, M.D., Ph.D.

Chair

Department of Microbiology
School of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania 19104
(Term expires June 30, 2005)

Gerald H. Friedland, M.D.

Director

AIDS Program
Yale-New Haven Hospital
Yale University School of Medicine
New Haven, Connecticut 06510
(Term expires June 30, 2007)

Diane V. Havlir, M.D.

Associate Professor of Medicine
San Francisco General Hospital
San Francisco, California 94110
(Term expires June 30, 2004)

Nancy B. Kiviat, M.D.

Chief
Department of Pathology
University of Washington
Harborview Medical Center
Seattle, Washington 98104-2499
(Term expires June 30, 2006)

Daniel R. Kuritzkes, M.D.

Director of AIDS Research
Partners AIDS Research Center
Cambridge, Massachusetts 02139
(Term expires June 30, 2005)

Marta L. Marthas, Ph.D.

Associate Adjunct Professor
California National Primate Research Center
School of Veterinary Medicine
University of California, Davis
Davis, California 95616
(Term expires June 30, 2005)

James D. Neaton, Ph.D.

Professor
Division of Biostatistics
School of Public Health
University of Minnesota
Minneapolis, Minnesota 55414
(Term expires June 30, 2004)

Alagarsamy Srinivasan, Ph.D.

Professor
Department of Microbiology and Immunology
Thomas Jefferson University
Philadelphia, Pennsylvania 19107
(Term expires June 30, 2005)

Wayne A. Tompkins, Ph.D.

Director of Graduate Programs
North Carolina State University
College of Veterinary Medicine
Raleigh, North Carolina 27606
(Term expires June 30, 2004)

Charles Wood, Ph.D.

Director and Professor
Nebraska Center for Virology
University of Nebraska Lincoln
School of Biological Sciences
Lincoln, Nebraska 68588-0666
(Term expires June 30, 2007)

Susan B. Zolla-Pazner, Ph.D.

Professor
Department of Pathology
New York University School of Medicine
New York, New York 10016
(Term expires June 30, 2007)

Scientific Review Administrator

Roberta Binder, Ph.D.

Scientific Review Administrator
Division of Extramural Activities
Acquired Immunodeficiency Syndrome Research
Review Committee
National Institute of Allergy and Infectious
Diseases
National Institutes of Health
Bethesda, Maryland 20892

AIDS RESEARCH ADVISORY COMMITTEE

The AIDS Research Advisory Committee is mandated by Public Law 100–607, the Health Omnibus Programs Extension of 1988 (HOPE legislation), which was signed into law November 4, 1988. The Committee advises and makes recommendations to the Director, NIAID, and to the Director, Division of Acquired Immunodeficiency Syndrome (DAIDS), in all areas of biomedical research on HIV infection and AIDS related to the mission of DAIDS, including pathogenesis, natural history, and transmission of HIV disease, and to those efforts that support progress in the detection, treatment, and prevention of HIV disease.

The Committee provides broad scientific, programmatic, and budgetary advice on all aspects of HIV-related research supported by NIAID, including fundamental basic and clinical research, discovery and development of vaccines and other preventive interventions, and training of researchers in these activities. The Committee's activities include the review of progress and productivity of ongoing efforts, assistance in identifying critical gaps/obstacles to progress, and approval of concepts for new initiatives.

The AIDS Research Advisory Committee roster is located online at www.niaid.nih.gov/facts/arac.htm.

Roster

King Holmes, M.D., Ph.D. (Chair)

Director, Center for AIDS and STDs
University of Washington
Seattle, Washington 98104
(Term expires June 30, 2005)

Moises Agosto

Health Care Communications Consultant
New York, New York 10016
(Term expires June 30, 2005)

Susan Buchbinder, M.D.

Director, San Francisco Department of Health
HIV Research Section
San Francisco, California 94102
(Term expires June 30, 2008)

Charles E. Davis, Jr., M.D.

Assistant Professor of Medicine
Institute of Human Virology
University of Maryland School of Medicine
Baltimore, Maryland 21201
(Term expires October 31, 2006)

Jay Brooks Jackson, M.D.

Professor and Director
Department of Pathology
Johns Hopkins Medical Institutions
Baltimore, Maryland 21287
(Term expires October 31, 2007)

Phyllis J. Kanki, D.V.M., S.D.

Professor of Immunology and Infectious Diseases
Harvard School of Public Health
Boston, Massachusetts 02115
(Term expires June 20, 2006)

Jeffrey Lennox, M.D.

Associate Professor of Medicine
Emory University School of Medicine
Grady Infectious Disease Program
Atlanta, Georgia 30322
(Term expires June 30, 2008)

Dorothy E. Lewis, Ph.D.

Professor, Department of Immunology
Baylor College of Medicine
Houston, Texas 77030
(Term expires October 31, 2005)

David Margolis, M.D.

Associate Professor

University of Texas Southwestern Medical Center
Division of Infectious Diseases
Dallas, Texas 75390
(Term expires June 30, 2008)

Reverend Raymond C. O'Brien

Professor of Law

Columbus School of Law
Catholic University of America
Washington, DC 20064
(Term expires October 31, 2006)

Andrea J. Ruff, M.D.

Associate Professor of International Health

Johns Hopkins University School of Hygiene and Health
Baltimore, Maryland 21287
(Term expires June 30, 2005)

Ruth Ruprecht, Ph.D., M.D.

Chief, Laboratory of Viral Pathogenesis

Dana-Farber Cancer Institute
Boston, Massachusetts 02115
(Term expires October 31, 2007)

Nathan M. Thielman, M.D., M.P.H.

Medical Director for Infectious Diseases

HIV Clinic
Duke University Medical Center
Durham, North Carolina 27710
(Term expires October 31, 2007)

Ex-Officio Members

Deborah L. Birx, M.D.

Director, U.S. Military HIV Research Program

Walter Reed Army Institute of Research
Rockville, Maryland 20850

Janet Collins, Ph.D.

Acting Director

National Center for HIV, STD, and TB
Prevention
Centers for Disease Control and Prevention
Atlanta, Georgia 30333

Lawrence R. Deyton, M.D.

Chief, Public Health

U.S. Department of Veterans Affairs
Washington, DC 20420

Henry Masur, M.D.

Chief, Critical Care Medicine

NIH Clinical Center
Bethesda, Maryland 20892

Jack Whitescarver, Ph.D.

Director, Office of AIDS Research

National Institutes of Health
Bethesda, Maryland 20892

Office of AIDS Research Advisory Council Liaison

Ashley T. Haase, M.D.

Regents' Professor and Head Department of Microbiology

University of Minnesota Medical School
Minneapolis, Minnesota 55455

AIDS VACCINE RESEARCH WORKING GROUP

The AIDS Vaccine Research Working Group, established in February 1997, assists in developing a comprehensive research program for expediting the discovery and development of an HIV vaccine. The individuals in this group provide advice regarding the vaccine research programs at the NIH with respect to scientific opportunities, gaps in knowledge, and future directions of research. The Working Group, which reports to the NIAID Council, is chaired by Dr. Barton Haynes and is composed of individuals with expertise in immunology, structural biology, virology, animal models, and vaccine development.

The AIDS Vaccine Research Working Group roster is located at the Web site: www.niaid.nih.gov/daids/vaccine/avrc.htm.

Roster

Barton F. Haynes, M.D. (Chair)
Frederic M. Hanes Professor and Chair
Department of Medicine
School of Medicine
Duke University
Durham, North Carolina 27710

R. Gordon Douglas, Jr., M.D.
Consultant
Vaccines, Infectious Diseases, and Global Health
Princeton, New Jersey 08540

Emilio A. Emini, Ph.D.
Senior Vice President
International AIDS Vaccine Initiative (IAVI)
New York, New York 10038

Scott Hammer, M.D.
Chief of Infectious Diseases
Columbia University Health Sciences
New York, New York 10032

Stephen C. Harrison, Ph.D.
Investigator, Howard Hughes Medical Institute
Professor of Biochemistry
Harvard University
Cambridge, Massachusetts 02138

Eric Hunter, Ph.D.
Professor of Microbiology
University of Alabama at Birmingham
Birmingham, Alabama 35294

Bette Korber, Ph.D.
Staff Scientist
Los Alamos National Laboratory
Los Alamos, New Mexico 87545

John P. Moore, Ph.D.
Professor of Microbiology and Immunology
Joan and Sanford I. Weill Medical College of
Cornell University
New York, New York 10021

Neal Nathanson, M.D.
Vice Provost for Research
University of Pennsylvania Medical Center
Philadelphia, Pennsylvania 19104

Douglas Richman, M.D.
Professor
University of California at San Diego
La Jolla, California 92093

Jerald Sadoff, M.D.
President and Chief Executive Officer
Aeras Global TB Vaccine Foundation
Rockville, Maryland 20850

Steven Wakefield

Associate Director, Community Relations and Education

HIV Vaccine Trials Network (HVTN)
Seattle, Washington 98109

David Watkins, Ph.D.

Professor of Pathology and Laboratory Medicine
University of Wisconsin-Madison Graduate School

Madison, Wisconsin 53715-1299

James Bradac, Ph.D.

Chief, Preclinical Research and Development Branch
Division of AIDS (DAIDS)
Bethesda, Maryland 20817

Margaret Johnston, Ph.D.

Director, Vaccine and Prevention Research Program
Division of AIDS (DAIDS)
Bethesda, Maryland 20817

Edmund Tramont, M.D.

Director
Division of AIDS (DAIDS)
Bethesda, Maryland 20817

Ex Officio Members

Deborah Birx, M.D.

Director, Division of Retrovirology
Walter Reed Army Institute of Research
U.S. Military HIV Research Program
Rockville, Maryland 20850

Lawrence Corey, M.D.

Fred Hutchinson Cancer Research Center
University of Washington
Seattle, Washington 98109

Karen Goldenthal, M.D.

Food and Drug Administration
Rockville, Maryland 20852

Alan Greenberg, M.D.

Chief, Epidemiology Branch
Centers for Disease Control and Prevention
Atlanta, Georgia 30333

ALLERGY, IMMUNOLOGY, AND TRANSPLANTATION RESEARCH COMMITTEE

The Allergy, Immunology, and Transplantation Research Committee advises the Director, NIH, and the Director, NIAID, with respect to programs and activities in the areas of allergy, clinical immunology, immunopathology, immunobiology, immunogenetics, immunochemistry, and transplantation biology. The Committee provides primary review of grant applications and special research programs. These include program projects, institutional National Research Service Awards, conference grants, and special developmental award programs. The Committee recommends ratings for applications that it determines to have significant and substantial scientific merit.

The Allergy, Immunology, and Transplantation Research Committee roster is located at the Web site www.niaid.nih.gov/facts/revcom.htm#CVH16.

Roster

David P. Huston, M.D. (Chair)

Cullen Chair in Immunology

Departments of Medicine, Microbiology, and Immunology

Baylor College of Medicine

Houston, Texas 77030

(Term expires June 30, 2004)

Rafeul Alam, M.D., Ph.D.

Professor and Director

Veda and Chauncey Ritter Chair in Immunology

National Jewish Medical and Research Center

Division of Allergy and Immunology

Denver, Colorado 80206

(Term expires June 30, 2004)

Randy R. Brutkiewicz, Ph.D.

Assistant Professor

Department of Microbiology and Immunology

Indiana University School of Medicine

Indianapolis, Indiana 46202

(Term expires June 30, 2006)

William J. Burlingham, Ph.D.

Associate Professor

Department of Surgery

University of Wisconsin Medical School

Madison, Wisconsin 53792

(Term expires June 30, 2005)

Daniel H. Conrad, Ph.D.

Professor

Department of Microbiology and Immunology

Virginia Commonwealth University

Richmond, Virginia 23928

(Term expires June 30, 2004)

Kathryn Haskins, Ph.D.

Professor

Department of Immunology

University of Colorado Health Sciences Center

Denver, Colorado 80106

(Term expires June 30, 2005)

Peter S. Heeger, M.D.

Associate Professor

Department of Immunology

Lerner Research Institute

Cleveland Clinic Foundation

Cleveland, Ohio 44195

(Term expires June 30, 2007)

Alan D. Levine, Ph.D.

Professor

Division of Gastroenterology

Department of Medicine

School of Medicine

Case Western Reserve University

Cleveland, Ohio 44106

(Term expires June 30, 2006)

Shoshana Levy, Ph.D.*Professor*

Department of Medicine/Oncology
 School of Medicine
 Stanford University
 Stanford, California 94305
 (Term expires June 30, 2005)

Nicholas W. Lukacs, Ph.D.*Associate Professor*

Department of Pathology
 School of Medicine
 University of Michigan
 Ann Arbor, Michigan 48109
 (Term expires June 30, 2005)

Kamal D. Moudgil, M.D., Ph.D.*Associate Professor*

Department of Microbiology and Immunology
 University of Maryland School of Medicine
 Baltimore, Maryland 21201
 (Term expires June 30, 2007)

Andre E. Nel, M.D., Ph.D.*Professor of Medicine*

Department of Medicine
 School of Medicine
 University of California, Los Angeles
 Los Angeles, California 90095
 (Term expires June 30, 2004)

Nancy J. Olsen, M.D.*Professor*

Division of Rheumatology
 Department of Medicine
 Vanderbilt University
 Nashville, Tennessee 37232
 (Term expires June 30, 2006)

Dhavalkumar D. Patel, M.D., Ph.D.*Professor of Medicine*

Department of Medicine
 University of North Carolina at Chapel Hill
 Chapel Hill, North Carolina 27599
 (Term expires June 30, 2007)

Shiguang Qian, M.D.*Associate Professor*

Department of Surgery
 Thomas E. Starzl Transplantation Institute
 University of Pittsburgh Medical School
 Pittsburgh, Pennsylvania 15213
 (Term expires June 30, 2005)

Liisa K. Selin, M.D., Ph.D.*Associate Professor*

Department of Pathology
 University of Massachusetts Medical School
 Worcester, Massachusetts 01655
 (Term expires June 30, 2007)

Mark J. Soloski, Ph.D.*Professor of Medicine*

Division of Rheumatology
 Department of Medicine
 The Johns Hopkins University School of
 Medicine
 Baltimore, Maryland 21205
 (Term expires June 30, 2007)

Anne M. VanBuskirk, Ph.D.*Assistant Professor*

Department of Surgery
 College of Medicine
 Ohio State University
 Columbus, Ohio 43210
 (Term expires June 30, 2004)

**Scientific Review Administrator
And Executive Secretary****Quirijn Vos, Ph.D.***Scientific Review Administrator*

Allergy, Immunology, and Transplantation
 Review Committee
 National Institute of Allergy and Infectious
 Diseases
 Bethesda, Maryland 20892

MICROBIOLOGY AND INFECTIOUS DISEASES RESEARCH COMMITTEE

The Microbiology and Infectious Diseases Research Committee advises the Director, NIH, and the Director, NIAID, with respect to programs and activities in microbiology and infectious diseases. Specialized areas of concern include molecular biology, microbial chemistry, parasitology, virology, bacteriology, mycology, vaccine development, and antimicrobial chemotherapy. The Committee provides a primary review of grant applications, cooperative agreements, and contract proposals for special research programs. These include program projects and centers, institutional National Research Service Awards, conference grants, and special developmental award programs in the areas mentioned above. The Committee recommends ratings for applications and proposals that it determines to have significant and substantial scientific merit and advises the Institute Director on the development of new programs in these scientific areas.

The Microbiology and Infectious Diseases Research Committee roster is located online at www.niaid.nih.gov/facts/revcom.htm#SAL32.

Roster

Randall K. Holmes, M.D., Ph.D. (Chair)

Professor and Chair

Department of Microbiology
University of Colorado Health Sciences Center
Denver, Colorado 80262
(Term expires June 30, 2004)

Michael J. Buchmeier, Ph.D.

Professor

Department of Neuropharmacology
The Scripps Research Institute
La Jolla, California 92037
(Term expires June 30, 2005)

Arturo Casadevall, M.D., Ph.D.

Professor

Department of Medicine
Albert Einstein College of Medicine
Bronx, New York 10461
(Term expires June 30, 2005)

Kyong-Mi M. Chang, M.D.

Assistant Professor of Medicine

Department of Medicine
Division of Gastroenterology
University of Pennsylvania
Philadelphia, Pennsylvania 19104-6144
(Term expires June 30, 2006)

Joshua Fierer, M.D.

Professor

Department of Medicine and Pathology
VA Health Care, San Diego
University of California, San Diego
San Diego, California 92161
(Term expires June 30, 2006)

Sharon L. Hillier, Ph.D.

Professor and Chair

Department of Obstetrics, Gynecology and
Reproductive Sciences
Magee-Women's Hospital
Pittsburgh, Pennsylvania 15213
(Term expires June 30, 2006)

David C. Hooper, M.D.

Associate Professor of Medicine

Infection Control Unit
Division of Infectious Diseases
Massachusetts General Hospital
Boston, Massachusetts 02114-2696
(Term expires June 30, 2007)

David J. Kusner, M.D., Ph.D.

Associate Professor

Department of Internal Medicine and
Immunology
University of Iowa
Iowa City, Iowa 52242
(Term expires June 30, 2007)

George K. Lewis, Ph.D.

Professor and Director

Division of Vaccine Research
Institute of Human Virology
University of Maryland Biotechnology Institute
Baltimore, Maryland 21201
(Term expires June 30, 2006)

Yvonne A. Maldonado, M.D.

Associate Professor

Department of Pediatrics
Stanford University School of Medicine
Stanford, California 94305
(Term expires June 30, 2006)

John D. McKinney, Ph.D.

Associate Professor

Laboratory of Infection Biology
The Rockefeller University
New York, New York 10021-6399
(Term expires June 30, 2007)

Diane M. McMahon-Pratt, Ph.D.

Professor

Department of Epidemiology and Public Health
Yale University School of Medicine
New Haven, Connecticut 06510
(Term expires June 30, 2004)

William A. Petri, Jr., M.D., Ph.D.

Professor

Department of Medicine and Infectious Diseases
University of Virginia Health System
Charlottesville, Virginia 22908
(Term expires June 30, 2005)

Stanley M. Spinola, M.D.

Director

Division of Infectious Diseases
Department of Medicine
Indiana University
Indianapolis, Indiana 46202
(Term Expires June 30, 2007)

John J. Treanor, M.D.

Professor

Department of Infectious Diseases Unit
University of Rochester School of Medicine
Rochester, New York 14642
(Term expires June 30, 2004)

Scientific Review Administrator

Gary Madonna, Ph.D.

Scientific Review Administrator

Microbiology and Infectious Diseases Research
Committee
National Institute of Allergy and Infectious
Diseases
National Institutes of Health
Bethesda, Maryland 20892

BOARD OF SCIENTIFIC COUNSELORS

The Board of Scientific Counselors advises the Director, NIH; the Deputy Director for Intramural Research, NIH; the Director, NIAID; and the Director, Division of Intramural Research (DIR), NIAID, concerning the Institute's intramural research programs. The Board's recommendations are based on rigid and objective reviews of NIAID laboratories to assess ongoing research as well as future directions and to evaluate the productivity and performance of NIAID's tenured scientists and tenure-track scientists. Following each review, the written report from the Board is forwarded, with a response from the Director, DIR, NIAID, to the Deputy Director for Intramural Research, NIH. In addition, the Board's recommendations are communicated annually to the National Advisory Allergy and Infectious Diseases Council.

The Board's review process strengthens NIAID's tenure system and the overall quality of the Institute's research. As a result of the Board's scientific review, NIAID may modify or redirect its intramural research priorities to allow for scientific growth of investigators as well as pursuit of important new areas of research. Its findings have a direct impact on the allocation of personnel, budget, and space resources within each laboratory.

The Board of Scientific Counselors roster is located at the Web site www.niaid.nih.gov/facts/bscroste.htm.

Roster

Barbara A. Osborne, Ph.D. (Chair)

Professor

Department of Veterinary and Animal Sciences
University of Massachusetts
Amherst, Massachusetts 01003
(Term expires June 30, 2005)

Richard J. Whitley, M.D. (Co-Chair)

Loeb Chair in Pediatrics

Professor of Pediatrics, Microbiology, and
Medicine
University of Alabama at Birmingham
Children's Hospital
Department of Pediatrics
Birmingham, Alabama 35233
(Term expires June 30, 2005)

Frances M. Brodsky, D.P.H.L.

Professor

Departments of Biopharmaceutical Sciences,
Pharmaceutical Chemistry, and Microbiology
and Immunology
G.W. Hooper Foundation
University of California at San Francisco
San Francisco, California 94143
(Term expires June 30, 2004)

George V. Hillyer III, Ph.D.

Professor and Director

Rio Piedras Campus
University of Puerto Rico
San Juan, Puerto Rico 00931
(Term expires June 30, 2004)

Scott Koenig, M.D., Ph.D.

President and Chief Executive Officer

MacroGenics, Inc.
1500 E. Gude Drive
Rockville, Maryland 20850
(Term expires June 30, 2008)

Steven L. Kunkel, Ph.D.

Endowed Professor in Pathology Research
M5214 Medical Science 1
1301 Catherine Street
Ann Arbor, Michigan 48109-0602
(Term expires June 30, 2008)

Robert S. Munford, M.D.

Jan and Henri Bromberg Chair in Internal Medicine
Department of Internal Medicine
University of Texas Southwestern Medical Center
Dallas, Texas 75390
(Term expires June 30, 2004)

Laurence A. Turka, M.D.

C. Mahlon Kline Professor of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania 19104
(Term expires June 30, 2007)

Janis J. Weis, Ph.D.

Professor
Division of Cell Biology and Immunology
Department of Pathology
University of Utah School of Medicine
Salt Lake City, Utah 84132
(Term expires June 30, 2007)

Executive Secretary

Thomas J. Kindt, Ph.D.

Director
Division of Intramural Research
National Institute of Allergy and Infectious
Diseases
National Institutes of Health
Bethesda, Maryland 20892

NIAID EXECUTIVE COMMITTEE

The Executive Committee is the senior internal policy and advisory group to the Director, NIAID, and acts as a forum for discussing and setting important Institute-wide scientific and management policies and discussing special issues and concerns that affect NIAID programs. As such, the Executive Committee consists of NIAID senior scientific and management staff, as well as several ad hoc members who provide program staff-level input. All new, expansion, and renewal program initiatives are reviewed by the Executive Committee at the earliest possible stage of project development to provide the NIAID Director and senior staff the opportunity to discuss and consider the merit and relationship of all projects to the ongoing programs of the Institute. The Executive Committee also serves as the vehicle for senior NIAID management to communicate with Institute program staff regarding issues and policies that are being considered for implementation at both the NIAID and NIH levels.

The Executive Committee roster is located at the Web site www.niaid.nih.gov/facts/executivecom.htm.

Roster

Anthony S. Fauci, M.D. (Chair)

Director

NIAID

H. Clifford Lane, M.D.

Acting Deputy Director

NIAID

Director

Office of Clinical Research

Art Bennett

Director

Office of Ethics

Juli Brown

Acting Director

Office of Management for New Initiatives

Susan Cook

Acting Director

Office of Administrative Services

Chief

Management Services Branch

Laurie K. Doepel

Acting Director

Office of Communications and Public Liaison

Gregory K. Folkers

Special Assistant for Research Reporting

Office of the Director

Dean Follmann, Ph.D.

Assistant Director for Biostatistics

Office of Clinical Research

Robin Gruber, M.P.S.

Special Assistant to the Director

Office of the Director

Hillery A. Harvey, Ph.D.

Special Assistant to the Director

Office of the Director

Carole A. Heilman, Ph.D.

Director

Division of Microbiology and Infectious Diseases

Lynn C. Hellinger

Associate Director for Management and Operations

Acting Executive Officer

Carole Hudgings, Ph.D.

Senior Advisor to the Deputy Director

Office of the Director

Thomas J. Kindt, Ph.D.

Director

Division of Intramural Research

Karin Lohman, Ph.D.

Acting Director
Office of Policy Analysis

John J. McGowan, Ph.D.

Director
Division of Extramural Activities

Margaret A. Moore

Chief of Staff
Office of the Director

Michael Mowatt, Ph.D.

Director
Office of Technology Development

Gary Nabel, M.D., Ph.D.

Director
Vaccine Research Center

Daniel Rotrosen, M.D.

Director
Division of Allergy, Immunology, and
Transplantation

Susan E. Sherman

Senior Attorney
Office of the General Counsel, NIH Branch

Ernie Takafuji, M.D., Ph.D.

Assistant Director for Biodefense Research
Office of the Director
Director
Office of Biodefense Research
Division of Microbiology and Infectious Diseases

Ralph Tate

Director
Office of Financial Management

Mike Tartakovsky

Chief Information Officer
Director
Office of Technology Information Systems

Nancy Touchette, Ph.D.

Special Assistant to the Director
Office of the Director

Edmund C. Tramont, M.D.

Director
Division of Acquired Immunodeficiency
Syndrome

Charlene Watson

Chief
Office of Human Resources, Branch D

Karl A. Western, M.D., D.T.P.H.

Assistant Director for International Research
Director
Office of Global Affairs

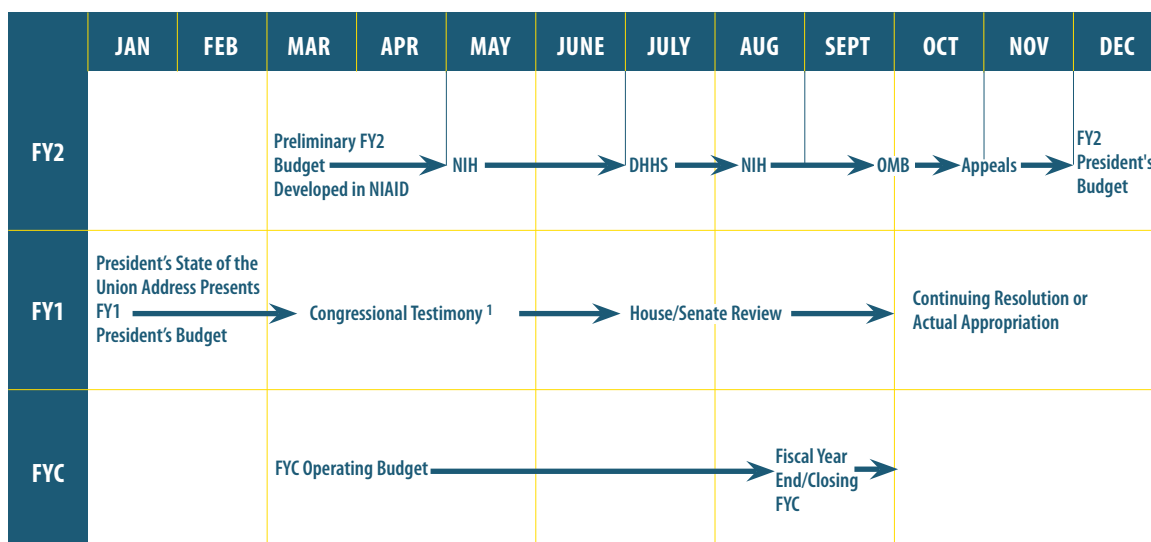
Executive Secretary

Ellie Menser

Executive Secretary
Office of Policy Analysis
6610 Rockledge Drive
Bethesda, Maryland 20892
emenser@niaid.nih.gov
301-435-8614

BUDGET OVERVIEW AND HISTORICAL TRENDS

FEDERAL BUDGET PROCESS



FISCAL YEAR = OCTOBER 1 TO SEPTEMBER 30

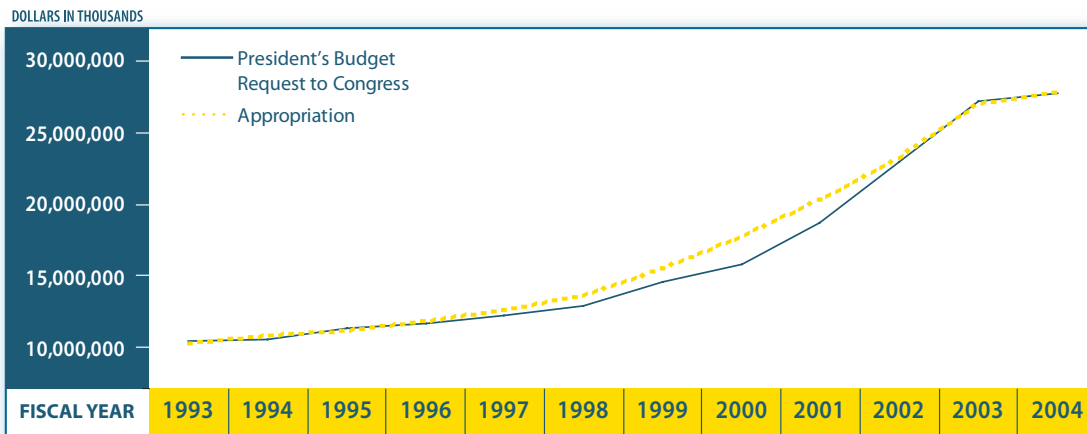
FY2 = SECOND FUTURE FISCAL YEAR

FY1 = FIRST FUTURE FISCAL YEAR

FYC = CURRENT FISCAL YEAR

¹ NIH Director and NIH Institute and Center Directors, including Director, NIAID, provide congressional testimony to the House and Senate Appropriations Subcommittees on Labor, Health and Human Services, and Education.

NIH APPROPRIATIONS HISTORY: FY 1993–2004



Fiscal Year	President's Budget Request to Congress	House Allowance	Senate Allowance	Appropriation ^a
(Dollars in Thousands)				
1993	10,579,684,000	10,368,551,000	10,387,721,000	10,326,604,000 ^b
1994	10,667,984,000	10,936,652,000	10,952,389,000	10,937,653,000 ^c
1995	11,473,000,000	11,322,023,000	11,333,181,000	11,299,522,000 ^d
1996	11,773,066,000	11,939,001,000	11,639,204,000	11,927,562,000 ^e
1997	12,406,300,000 ^f	12,747,203,000	12,414,580,000 ^g	12,740,843,000 ^h
1998	13,078,203,000 ⁱ	13,505,294,000	13,692,844,000	13,674,843,000 ^{j, k}
1999	14,763,313,000 ^l	14,862,023,000	15,622,386,000	15,629,156,000 ^m
2000	15,932,786,000	16,964,547,000	17,613,470,000	17,820,587,000 ⁿ
2001	18,812,735,000	20,512,735,000	20,512,735,000	20,458,130,000 ^{o, p}
2002	23,112,130,000	22,945,199,000	23,765,488,000	23,296,382,000 ^{q, r}
2003	27,343,417,000 ^{s, t}	27,351,717,000	27,369,000,000 ^u	27,066,782,000 ^{t, v}
2004	27,892,765,000 ^t	26,043,991,000	28,369,548,000	27,887,512,000 ^w

a Reflects enacted supplements, rescissions, and reappropriations.

b Reflects enacted administrative reductions of an across-the-board 0.8 percent of \$83,571,000, \$34,857,000 for salaries and expenses, and a consultant services reduction of \$1,342,000. All columns adjusted to include transfer from ADAMHA.

c Reflects a salaries and expense rescission of \$18,120,000. Excludes \$1,000,000 supplemental in NCRR for earthquake relief.

d Includes \$1,299,328,000 for NIH research appropriated to the NIH Office of AIDS Research. Reflects enacted reductions of \$7,446,000 for procurement, \$345,000 for rent, and 4,401,000 for bonus pay, and rescission of \$10,000,000 in NCRR for construction and \$12,384,000 in administrative costs.

e Includes \$1,410,925,000 appropriated to the ICs for HIV research. Incorporates the NIH share of the Government-wide administrative cost rescission (\$5,780,000) and the Labor/HHS/Education bonus pay rescission (\$5,659,000).

f Includes \$1,431,908,000 for HIV research in the NIH Office of AIDS Research.

g Includes \$1,460,312,000 for HIV research in the NIH Office of AIDS Research.

h Includes \$1,501,073,000 for HIV research in the NIH Office of AIDS Research. Incorporated the NIH share of the salaries and expenses reduction (\$6,140,000) and the public/legislative affairs reduction (\$220,000).

i Includes \$1,540,765,000 for HIV research in the NIH Office of AIDS Research.

j Includes \$1,607,053,000 appropriated to the ICs for HIV research.

k Beginning in FY 1998, the appropriation includes funds appropriated to NIDDK for Type 1 diabetes research.

l Reflects a decrease of \$34,530,000 for the budget amendment for bioterrorism. Includes \$1,728,099,000 for HIV research in the NIH Office of AIDS research.

m Includes \$1,800,046,000 appropriated to the ICs for HIV research. Includes \$10,230,000 for rescission.

n Includes \$2,024,956,000 appropriated to the ICs for HIV research. Includes \$99,883,000 for NIH share of across-the-board reduction and reflects \$20,000,000 transferred to CDC. Includes \$40,000,000 in forward funding appropriated in FY 1999.

o Includes \$2,244,987,000 appropriated to ICs for HIV research. Reflects NIH share of across-the-board reduction (\$8,666,000) and \$5,800,000 transferred to the DHHS.

p Beginning in FY 2001, VA/HUD began appropriating Superfund Research funds directly to NIEHS.

q Includes \$2,535,672,000 appropriated to the ICs for HIV research. Reflects NIH share of across-the-board reduction (\$9,273,000) and transfer of \$100M to the Global Fund for HIV/AIDS, malaria, and tuberculosis.

r Includes \$10.5 million appropriated from the Emergency Relief Fund.

s Excludes \$583,000 transferred to the Department of Homeland Security.

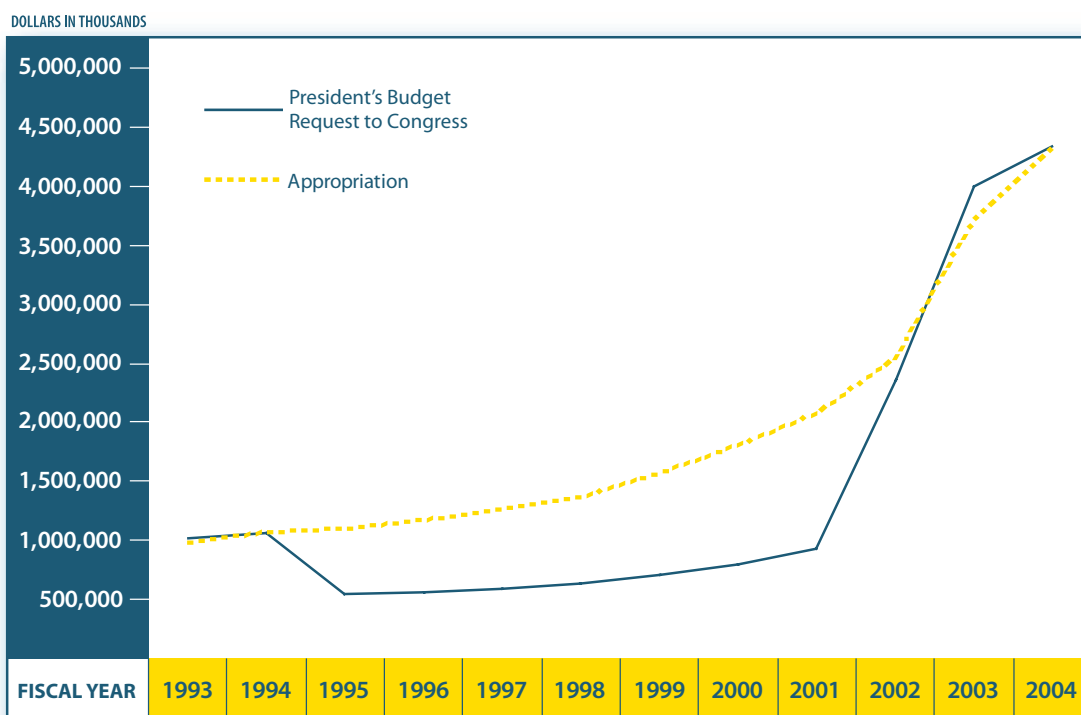
t Includes \$100 million in FY2003 and \$150 million in FY 2004 and FY 2005 authorized to NIDDK for Type 1 diabetes research.

u Includes \$97 million authorized to NIDDK for Type 1 diabetes research.

v Includes \$2,747,463,000 appropriated to the ICs for HIV research. Reflects NIH share of the across-the-board reduction (\$177,085,000), and transfers of \$99,350,000 to the Global Fund to Fight HIV/AIDS, Malaria, and Tuberculosis, and \$583,000 to the Department of Homeland Security.

w Includes \$2,850,581,000 appropriated to the ICs for HIV research. Reflects NIH share of the across-the-board reduction (\$165,459,000), Labor/HHS rescission (\$17,492,000), and transfer of \$149,115,000 to the Global Fund to Fight HIV/AIDS, Malaria, and Tuberculosis.

NIAID APPROPRIATIONS HISTORY: FY 1993–2004



Fiscal Year	President's Budget Request to Congress	House Allowance	Senate Allowance	Appropriation ^a
(Dollars in Thousands)				
1993	1,010,845	990,055	989,055	979,471 ^b
1994	1,065,583	1,065,583	1,065,583	1,063,704 ^c
1995	542,864 ^d	1,094,633	1,094,633	1,092,507 ^e
1996	557,354 ^d	1,169,628	1,139,326	1,171,168 ^f
1997	584,362 ^d	1,256,149	1,229,009	1,257,794 ^g
1998	634,272 ^d	1,339,459	1,359,688	1,352,119 ^h
1999	703,723 ^{d,i}	1,470,460	1,540,102	1,569,063
2000	789,156	1,694,019	1,786,718	1,797,988 ^j
2001	936,166	2,062,126 ^k	2,066,526	2,069,388
2002	2,355,325	2,337,204	2,375,836	2,535,788
2003	3,997,369	2,674,213	3,727,473	3,706,789
2004	4,335,255	4,440,007 ^l	4,456,300 ^m	4,303,040 ⁿ

a Reflects enacted supplements, rescissions, and reappropriations.

b Excludes an enacted administrative reduction of \$12,334,000.

c Includes rescission of \$1,879,000.

d Excludes funds for HIV research activities consolidated in the NIH Office of AIDS Research.

e Includes a rescission of \$1,293,000 and a transfer of \$458,000.

f Includes an enacted administrative reduction of \$1,145,000 and a net NIH Director's transfer of \$2,685.

g Includes a rescission of \$575,000 for administrative expenses and a net positive transfer of \$1,135,000 from the NIH Director's Reserve.

h Includes rescissions and transfers.

i Reflects an increase of \$1,683,000 for the budget amendment for biodefense.

j Includes a rescission amount of \$5,075,000.

k Represents program level.

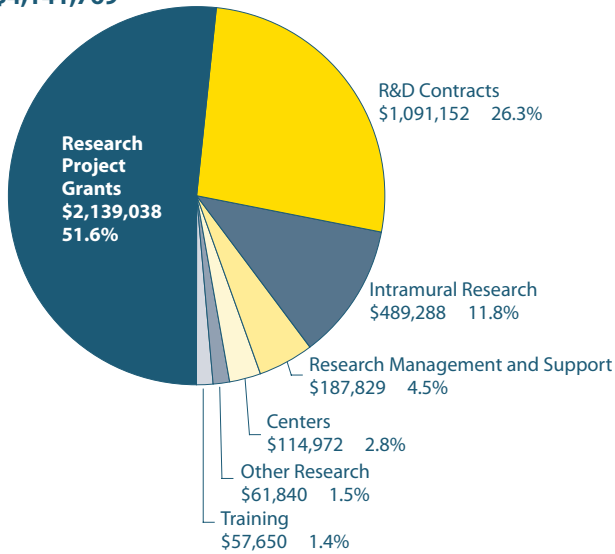
l Includes \$100M for the Global Fund to fight HIV/AIDS, Malaria, and Tuberculosis and \$14.5M for the Virtual VRC.

m Includes \$149M for the Global Fund to fight HIV/AIDS, Malaria, and Tuberculosis and \$14.5M for the Virtual VRC.

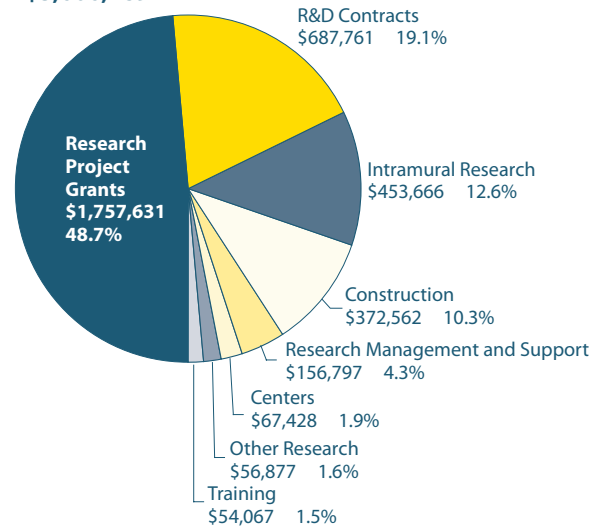
n Includes \$149M for the Global Fund to fight HIV/AIDS, Malaria, and Tuberculosis.

NIAID FUNDING BY BUDGET MECHANISM: **FY 2003–2004** *(Dollars in Thousands)*

Fiscal Year 2004
\$4,141,769



Fiscal Year 2003
\$3,606,789

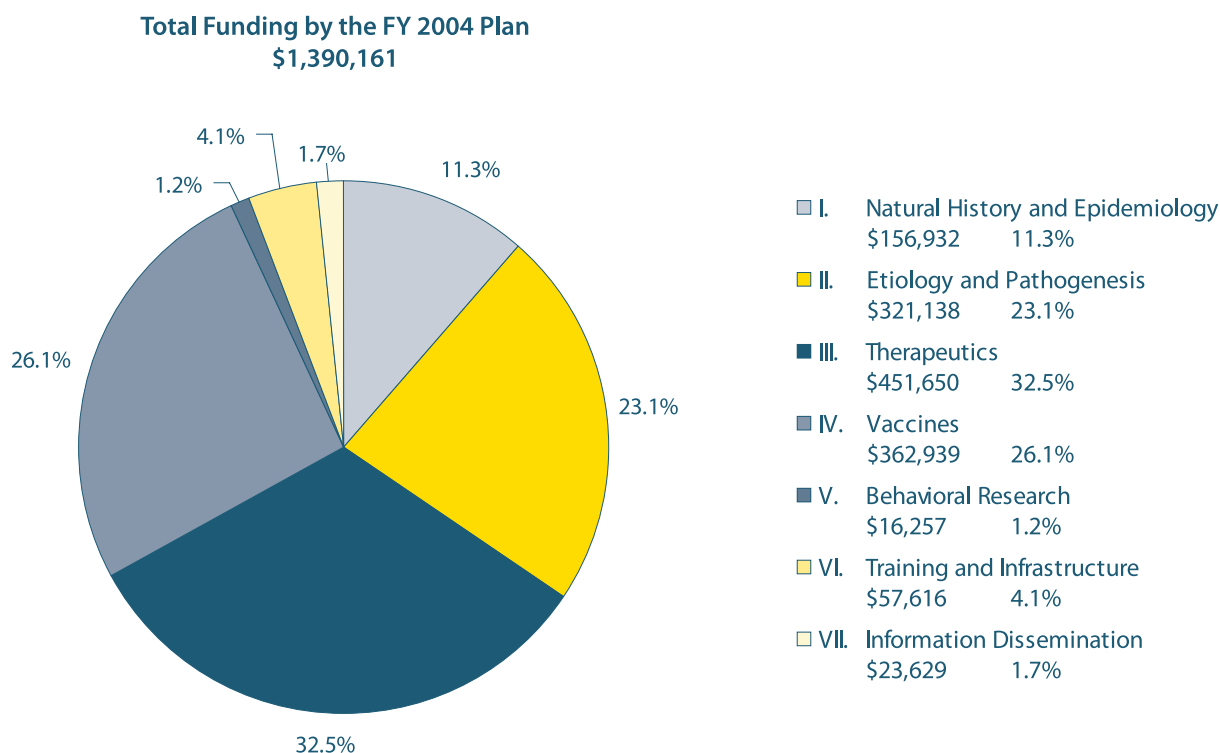


Budget Mechanism	FY 2003 ^a	% of Total	FY 2004 ^a	% of Total	% Change FY03 to FY04
Research Project Grants (RPGs)					
Noncompeting	\$1,286,067		\$1,486,283		
Competing	471,564		652,755		
Subtotal, RPGs	1,757,631	48.7	2,139,038	51.6	+2.9
Centers	67,428	1.9	114,972	2.8	+9
Other Research	56,877	1.6	61,840	1.5	-.1
Training	54,067	1.5	57,650	1.4	-.1
R&D Contracts	687,761	19.1	1,091,152	26.3	+7.2
Subtotal, Extramural	2,623,764		3,464,652		
Intramural Research	453,666	12.6	489,288	11.8	-.8
Research Management and Support	156,797	4.3	187,829	4.5	+.2
Construction	372,562	10.3	0	0	-10.3
Total	\$3,606,789		\$4,141,769		+14.83

^a Dollars in thousands and reflects actual obligations versus appropriations.

NIAID FUNDING BY THE FY 2004 NIH PLAN FOR HIV-RELATED RESEARCH^a

(Dollars in Thousands)

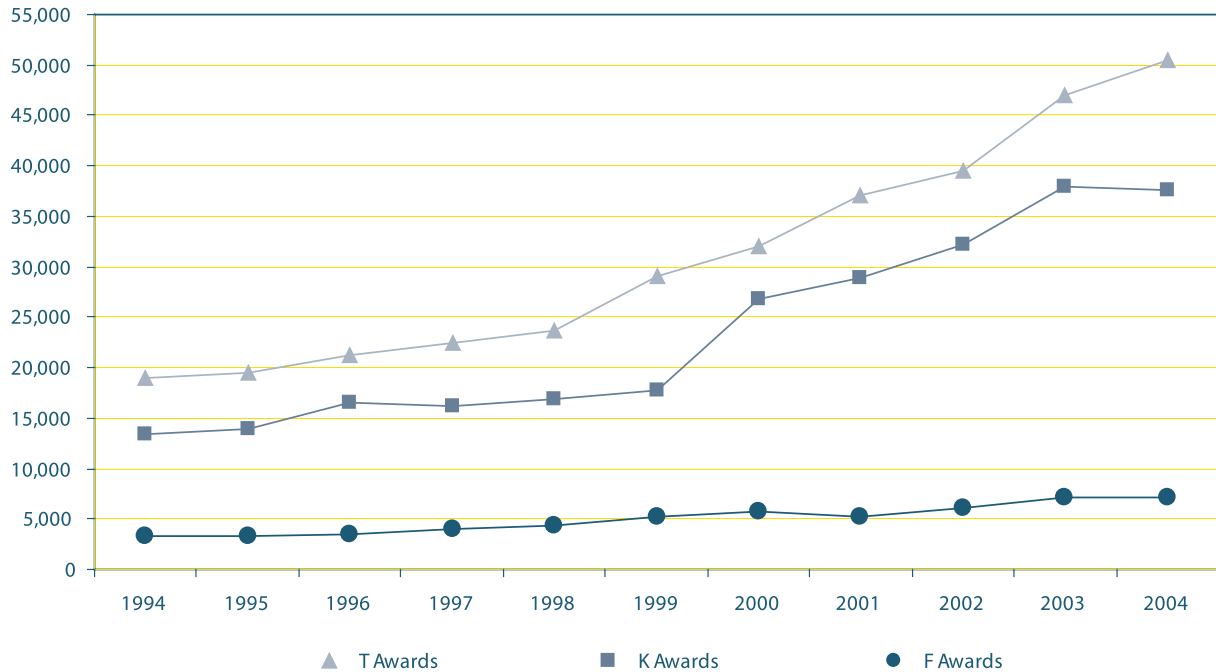


	FY 2004 Actual	
	Amount	Percent of Total
I. Natural History and Epidemiology	156,932	11.3%
II. Etiology and Pathogenesis	321,138	23.1%
III. Therapeutics	451,650	32.5%
IV. Vaccines	362,939	26.1%
V. Behavioral Research	16,257	1.2%
VI. Training and Infrastructure	57,616	4.1%
VII. Information Dissemination	23,629	1.7%
Total Funding by the FY 2004 Plan	1,390,161	100%

^a A comprehensive plan for HIV-related research developed by the NIH Office of AIDS Research and the NIH Institutes and Centers.

NIAID RESEARCH TRAINING AND CAREER AWARDS^a : FY 1994–2004

(Dollars in Thousands)



Fiscal Year	T Awards (Institutional Awards)		K Awards (Career Awards)		F Awards (Individual Training Awards)	
	No. Awards	Dollar Amount	No. Awards	Dollar Amount	No. Awards	Dollar Amount
1994	115	18,894	174	13,411	125	3,378
1995	118	19,539	176	13,884	124	3,386
1996	123	21,254	204	16,566	126	3,439
1997	140	22,478	204	16,159	150	4,067
1998	152	23,738	211	16,908	151	4,350
1999	148	29,092	205	17,686	146	5,177
2000	164	32,035	241	26,863	161	5,709
2001	923	37,113	245	28,885	146	5,266
2002	919	39,474	272	32,237	153	6,162
2003	1,014	46,936	309	38,030	163	7,108
2004	1,087	50,550	314	37,521	173	7,100

^a Includes F31, F32, F33, F34, K04, K06, K07, K08, K11, T32, T35, and T36 awards (described in the NIH Extramural Funding Mechanisms appendix).

APPENDICES

APPENDICES

LEGISLATIVE CHRONOLOGY

NOV. 1, 1948

The National Microbiological Institute was established under authority of section 202 of the Public Health Service Act, as implemented by General Circular No. 55, Organization Order No. 20, dated October 8, 1948.

DEC. 29, 1955

NIAID was established (replacing the National Microbiological Institute) under authority of the Omnibus Medical Research Act (Public Law 81-692, 64 Stat. L. 443), as implemented by a Public Health Service Briefing Memorandum of November 4, 1955, from the Surgeon General to the Secretary of Health, Education, and Welfare.

NOV. 4, 1988

NIAID was provided with additional authorities for AIDS research under Title II of the Health Omnibus Programs Extension of 1988 (HOPE legislation) (Public Law 100-07), the first major law to address AIDS research, information, education, and prevention.

AUG. 14, 1991

The Public Health Service Act was amended by Public Law 102-96, the Terry Beirn Community-Based AIDS Research Initiative Act of 1991, which reauthorized NIAID's Community Programs for Clinical Research on AIDS (CPCRA). CPCRA was renamed in honor of Mr. Beirn (an AIDS activist and congressional staffer who died in 1991) and was reauthorized for an additional 5 years.

JUNE 10, 1993

The Public Health Service Act was amended by Public Law 103-43, the National Institutes of Health Revitalization Act of 1993. This comprehensive legislation required NIAID to include research on tropical diseases in its mission statement and directs the Secretary, U.S. Department of Health and Human Services, to ensure that individuals with expertise in chronic fatigue syndrome or neuromuscular diseases are appointed to appropriate NIH advisory committees.

DEC. 14, 1993

The Preventive Health Amendments of 1993 were passed, which included provisions requiring the Director, NIAID, to conduct or support research and research training regarding the cause, early detection, prevention, and treatment of tuberculosis. (The Institute already had authority to conduct such research under its authorities in Title IV, Public Health Service Act.)

NOV. 29, 1999

The fiscal year 2000 Appropriations Act (Public Law 106-113) established the NIH Challenge Grants program to promote joint ventures between the NIH and the biotechnology, pharmaceutical, and medical device industries. A one-time funding level of \$20 million was provided within the Public Health and Social Services Emergency Fund.

OCT. 17, 2000

The Children's Health Act (Public Law 106-310) required the Directors of NIAID and the National Institute of Arthritis and Musculoskeletal and Skin Diseases to expand and intensify the activities of their Institutes with respect to research and related activities concerning juvenile arthritis and related conditions.

NOV. 13, 2000

The Public Health Improvement Act (Public Law 106-505) authorized the NIAID Director to establish a program of clinical research and training awards for sexually transmitted infections.

July 21, 2004

The Project Bioshield Act (Public Law 108-276) authorized the Director of NIH to employ expedited peer review procedures for grants, contracts, and cooperative agreements addressing qualified countermeasures research. In addition, the Act authorized the Director of NIAID to award grants or contracts to public and nonprofit private entities to expand, remodel, renovate, or alter existing research facilities or construct new facilities.

Previous Directors

Victor H. Haas, M.D., 1948–1957

Justin M. Andrews, Sc.D., 1957–1964

Dorland J. Davis, M.D., D.P.H., 1964–1975

Richard M. Krause, M.D., 1975–1984

TECHNOLOGY TRANSFER

Technology transfer in Federal laboratories facilitates the dissemination of new technologies and research materials developed by Government scientists. This technology transfer fuels further innovation and commercialization by the extramural research and development community, ultimately resulting in an improvement in the public health and an increase in the competitiveness of U.S. industry. Federal legislation mandates and defines the Government's technology transfer activities. The key pieces of legislation are the Federal Technology Transfer Act of 1986 and the National Technology Transfer and Advancement Act of 1995.

The NIAID Office of Technology Development (OTD) accomplishes technology transfer by facilitating the transfer of significant research advances and resources to the broader scientific community and the development of collaborative relationships between NIAID scientists, industry, and academia. NIAID uses various mechanisms to accomplish these ends, including Material Transfer Agreements (MTAs), Cooperative Research and Development Agreements (CRADAs), Materials-CRADAs (M-CRADAs), Confidential Disclosure Agreements (CDAs), Clinical Trial Agreements (CTAs), Drug Screening Agreements (DSAs), Collaboration Agreements (CAs), and, through the NIH Office of Technology Transfer (OTT), the patenting of inventions and the negotiation of various license agreements.

NIAID scientists report inventions to OTD by submitting Employee Invention Reports (EIRs). The EIRs are reviewed by OTD and, with the assistance of the NIAID Technology Evaluation Advisory Committee (TEAC), are evaluated for the purpose of filing domestic and foreign patent applications. In fiscal year (FY) 2004, TEAC reviewed 41 intramural EIRs and recommended that patent applications be filed on 26 of them.

NIAID currently has 386 active U.S. patent properties, including 209 issued patents and 177 pending patent applications.

NIAID had a total of 226 active license agreements in FY 2004 for both patented inventions and biological materials. These licenses generated about \$11 million in royalty income, which was first used to pay NIAID inventors their share according to Federal law and NIH policy. The Institute also distributed royalty income to intramural laboratories to support research projects and equipment acquisition that otherwise would not have been accomplished with appropriated funds. The remaining royalties were used to pay OTD's entire operating budget, including patent prosecution fees, OTD staff salaries, associated office expenses, and overhead charged by OTT.

In FY 2004, a total of 128 MTAs, 9 CTAs, 53 CDAs, 6 CRADAs, 12 M-CRADAs, 5 CAs, and 15 other agreements were executed and negotiated by OTD. NIAID extramural divisions referred technology transfer issues to OTD on 9 contracts, and OTD NIAID scientists performed research under 32 CRADAs and 38 M-CRADAs in FY 2004. The following table provides a history of NIAID's patent, license, and CRADA activities.

NIAID Technology Transfer Activities

Fiscal Year	Pending Patents	Issued Patents	Licenses In Effect	Active CRADAs
1992	77	48	65	21
1994	85	65	84	29
1995	96	71	101	31
1996	95	84	120	42
1997	128	91	131	71
1998	154	83	155	95
1999	169	94	195	74
2000	229	100	196	86
2001	194	125	190	93
2002	147	139	197	85
2003	174	168	245	71
2004	177	209	226	70

Technology Transfer Highlights

In FY 2004, OTD negotiated or facilitated the following public-private partnerships:

- **Development and selection of research-grade plasmid DNA vectors encoding West Nile virus proteins and formulations for potential use as prophylactic vaccines in human and veterinary applications (Vical)**
Investigators at the Vaccine Research Center (VRC), NIAID, and Vical, Incorporated will collaborate in the development and evaluation of West Nile Virus (WNV) DNA vaccine candidates. Recently, WNV DNA vaccines have shown promising protection in animal studies. The VRC and Vical will evaluate materials that might enhance or improve the immune response to WNV and select the best constructs and formulations of WNV DNA vaccine candidates appropriate for clinical development.
- **Evaluation of herpes simplex virus vectors encoding HIV-1 proteins (BioVex).** Herpes simplex virus (HSV) vectors are being investigated as a gene delivery system for gene therapy and vaccination. Recombinant HSV vectors offer a promising strategy for development of a candidate HIV-1 vaccine that could be effective in humans. Investigators at the Vaccine Research Center (VRC), National Institute of Allergy and Infectious Diseases, National Institute of Health, and BioVex, Ltd. will collaborate to evaluate and develop HSV vectors expressing VRC's modified HIV-1 genes. The collaboration will evaluate such HSV vectors for potential application as an HIV preventive or therapeutic vaccine. The VRC will provide BioVex with several modified HIV-1 genes, and BioVex will construct and produce recombinant HSV vectors that express VRC's HIV-1 genes utilizing the BioVex HSV system. The overall goal is to provide the VRC with advanced vector technologies suitable for rapid advancement toward clinical trial.
- ***In vitro* and *in vivo* evaluation of novel compounds with antitubercular activity (Anacor Pharmaceuticals).** Anacor Pharmaceuticals and the Tuberculosis Research Section of the Laboratory of Host Defenses, NIAID, NIH, are entering into a collaborative research and development agreement to screen promising candidate molecules for activity against *Mycobacterium tuberculosis*. These molecules have been shown to have a unique mechanism of action that targets problematic Gram-positive pathogens and members of this series. By providing selectivity for the treatment of tuberculosis these molecules may have utility in the chemotherapy of this important disease.
- **Development of prophylactic and therapeutic monoclonal antibodies to vaccinia/smallpox, SARS, and anthrax (MacroGenics).** Under this Cooperative Research and Development Agreement, investigators in the Laboratory of Infectious Diseases, the Laboratory of Viral Diseases, and the Bacterial Toxins and Therapeutics Section Division of Intramural Research at NIAID and MacroGenics, Inc., will attempt to isolate and characterize human and human-like neutralizing monoclonal antibodies to vaccinia virus, the SARS virus, and anthrax.
- **Identification of novel antitubercular agents through high-throughput screening (Exelixis).** The Tuberculosis Research Section of NIAID and Exelixis, Inc., are collaborating under this CRADA to screen compound libraries for potential new compounds active against *M. tuberculosis*, which can then be put forward for the treatment of tuberculosis.
- **Chlamydial antigen discovery (Chiron).** A cooperative approach will be used to

identify novel chlamydial antigens important to chlamydial vaccine development. The project involves the combination of *in vitro* models of cytokine mediated chlamydial persistent infection, isolation of HLA class I and II processed peptides from infected epithelial cells, elution of peptides from HLA

molecules, and identification of peptides and native proteins by high-throughput mass spectrometry. The identified peptides might represent unique hereto-undiscovered antigens important to protective cellular immune responses and future anti-chlamydial therapeutic strategies.

New CRADAs

During FY 2004, NIAID scientists entered into the following six new CRADAs:

Collaborator	Investigator	Title
Anacor Pharmaceuticals, Inc.	Clifton E. Barry III, Ph.D. Laboratory of Immunogenetics	<i>In Vitro</i> and <i>In Vivo</i> screening of Novel Antitubercular Agents.
BioVex, Ltd.	Phillip Gomez III, Ph.D., M.B.A. Vaccine Research Center	Evaluation of HSV Vectors Encoding HIV-1 Proteins.
Chiron Corp.	Harlan D. Caldwell, Ph.D., Laboratory of Intracellular Parasites	Chlamydia Antigen Discovery.
Exelixis, Inc.	Clifton E. Barry III, Ph.D. Laboratory of Immunogenetics	New Lead Discovery for the Identification of Novel Antitubercular Agents.
MacroGenics, Inc.	Robert H. Purcell, M.D. Laboratory of Infectious Diseases	Development of Prophylactic and Therapeutic Monoclonal Antibodies to Vaccinia/Smallpox, SARS, and Anthrax.
Vical, Inc.	Phillip Gomez III, Ph.D., M.B.A. Vaccine Research Center	Development And Selection Of Research-Grade Plasmid DNA Vectors Encoding West Nile Virus (WNV) Proteins And Formulations For Potential Use As Prophylactic Vaccines In Human And Veterinary Applications.

Ongoing CRADAs

In addition to the new CRADAs, research was done under the following ongoing CRADAs:

Collaborator	Investigator	Title
Achillion Pharmaceuticals NCI	John Inman, Ph.D. Laboratory of Immunology	Development of Optimized Inhibitors of Protein Zinc Finger Domains
Chiron	H. Clifford Lane, M.D. Laboratory of Immunoregulation	Research and Development of IL-2 as a Treatment for HIV Infection
Crucell	Phillip Gomez III, Ph.D., M.B.A. Vaccine Research Center	Development of an Improved Recombinant Adenovirus Vector for Vaccination Against the Ebola Virus
Genetics Institute	Ethan Shevach, M.D. Laboratory of Immunology	Analysis Of Gene Expression In Immunoregulatory T Cells That Co-Express The CD4 And CD25 Surface Markers

Collaborator	Investigator	Title
Genetics Institute	Thomas Wynn, Ph.D. Laboratory of Parasitic Disease	Development Of IL-13 Antagonism As A Treatment For Fibrosis In Schistosomiasis
Genetics Institute	Warren Strober, M.D. Peter Mannon, M.D. Ivan Fuss, M.D. Laboratory of Clinical Investigation	A Randomized, Double-Blind, Placebo-Controlled, Dose-Finding, Safety Study Of Two Parallel Dose Levels Of Subcutaneously Administered Human Monoclonal Antibody To Interleukin-12 (J695) In Patients With Active Crohn's Diseases
GenVec	Phillip Gomez III, Ph.D., M.B.A. Vaccine Research Center	Evaluation of Adenoviral Vectors Encoding HIV-1 Proteins
GenVec	Phillip Gomez III, Ph.D., M.B.A. Vaccine Research Center	Evaluation of Adenoviral Vectors Encoding Proteins Associated with SARS
Glaxo Research & Development	Clifton E. Barry III, Ph.D. Laboratory of Immunogenetics	Development of New Drugs for the Treatment of Tuberculosis
GlaxoSmithKline	Holli Hamilton, M.D., M.P.H. Barbara Savarese, R.N. Division of Microbiology and Infectious Diseases	A Double-Blind, Randomized, Controlled Phase III Study To Assess The Prophylactic Efficacy Of Rgd/Alum/MPL Vaccine In The Prevention Of Genital Herpes Disease In Young Sexually Active Women (DMID#01-643)
IAVI	Richard T. Wyatt, Ph.D. Vaccine Research Center	Rational Design of HIV Envelope Glycoprotein Variants for Structural and Immunological Analysis Using X-Ray Crystallography To Elicit Broadly Neutralizing HIV-1 Antibodies.
Ichor Medical Systems	Phillip Gomez III, Ph.D., M.B.A. Vaccine Research Center	Evaluation Of Electroporation-Mediated Delivery Of An HIV DNA Vaccine
Innogenetics	Robert H. Purcell, M.D. Laboratory of Infectious Diseases	Analysis of the Immune Response to Hepatitis C Virus
Invitrogen	Thomas Kindt, Ph.D. Michael Wilson, Ph.D. Research Technologies Branch, Division of Intramural Research	Oligonucleotide Control Sets for Microarray Applications
Maxygen	Louis Miller, M.D. Carole Long, Ph.D. Allan Saul, Ph.D. Laboratory of Parasitic Disease	Novel, Polyspecific Malaria Vaccine Development Based on PfEMP1 Using Molecular Breeding™ Directed Molecular Evolution Technologies
MedImmune Vaccines (formerly Aviron)	George Curlin, M.D. Division of Microbiology and Infectious Diseases	Development of a Live, Attenuated Cold-Adapted Influenza Vaccine
Merck	Gary Nabel, M.D., Ph.D. Vaccine Research Center	Development of an Adenoviral-Based HIV Vaccine
Merck	Stephen Straus, M.D. Laboratory of Clinical Investigation	A Double-Blind, Placebo-Controlled Study Of The Efficacy Of Live, Attenuated Oka/Merck Varicella Zoster Vaccine In Reducing The Incidence And/Or Severity Of Shingles In Adults

Collaborator	Investigator	Title
Merial	José Ribeiro M.D., Ph.D. Laboratory of Parasitic Disease	Evaluation Of DNA Vaccines Encoding Sand Fly Salivary Proteins As Candidates To Control <i>Leishmania Infantum</i> Infection In Dog
Nexell Therapeutics	Harry L. Malech, M.D. Mitchell Horwitz, M.D. Laboratory of Host Defenses	Study of Low Intensity Preparative Regimen Followed By HLA-Matched Transplantation for Chronic Disease
Novartis	Marshall Plaut, M.D. Division of Allergy, Immunology, and Transplantation	A Double-Blind, Placebo Controlled Study Of The Efficiency of E25 Anti-IgE Reducing Asthma Symptoms In Inner City Children
Novavax	Louis Miller, M.D. Laboratory of Parasitic Disease	Merozoite Surface Protein 1 Expressed in Insect Cells: Process Development, Preclinical and Initial Clinical Evaluation
Osel	Edward Berger, Ph.D. Laboratory of Viral Diseases	SCD4-17b Expressed By/On <i>Lactobacillus</i> As An Anti-HIV Topical Microbicide
Panacos	Eric Freed, Ph.D. Laboratory of Molecular Microbiology	A Study of the Mechanism of Action of the Anti-HIV Compound, PA-457
Quantum Dot	Mario Roederer, Ph.D. Vaccine Research Center	Use of Quantum Dots for Improved Cellular Classification in Flow Cytometry
Wyeth-Lederle Vaccines	Pamela McInnes, Ph.D. Division of Microbiology and Infectious Diseases	Preventing Childhood Mortality—An Efficacy Trial of a Pneumococcal Conjugate Vaccine in Upper and Central River Divisions, The Gambia

NIH EXTRAMURAL FUNDING MECHANISMS USED BY NIAID

Fellowship Programs

F31 Predoctoral Individual National Research Service Award (NRSA)—provides predoctoral individuals with supervised research training in specified health and health-related areas leading toward the research degree (e.g., Ph.D.).

F32 Postdoctoral Individual NRSA—provides postdoctoral research training to individuals to broaden their scientific background and extend their potential for research in specified health-related areas.

F33 NRSA for Senior Fellows—provides opportunities for experienced scientists to make major changes in the direction of their research careers, to broaden their scientific background, or to acquire new research capabilities.

F35 Intramural NRSA Individual Postdoctoral Program—supports a postdoctoral trainee in the NIH intramural program.

Research Career Programs

K02 Independent Scientist Award—provides support for newly independent scientists who can demonstrate the need for a period of intensive research focus as a means of enhancing their research careers.

K08 Clinical Investigator Award—provides the opportunity for promising medical scientists (with demonstrated aptitude to develop into independent investigators) or faculty members who will pursue research aspects of categorical areas applicable to the awarding unit, and aids in filling the important academic faculty

gap in these shortage areas within health professional institutions of the country.

K22 Career Transition Award—provides support to outstanding newly trained basic or clinical investigators to develop their independent research skills through a two-phase program: an initial period involving an intramural appointment of the NIH and a final period of support at an extramural institution. The award is intended to facilitate the establishment of a record of independent research by the investigator to sustain or promote a successful research career.

K23 Mentored Patient-Oriented Research Career Development Award—provides support for the career development of investigators who have made a commitment to focus their research endeavors on patient-oriented research. This mechanism provides support for a 3-year minimum up to a 5-year period of supervised study and research for clinically trained professionals who have the potential to develop into productive clinical investigators.

K24 Midcareer Investigator Award in Patient-Oriented Research—provides support for experienced clinicians to allow them protected time to devote to patient-oriented research and to act as mentors for beginning clinical investigators.

K25 Mentored Quantitative Research Career Development Award—supports junior faculty-level investigators with quantitative scientific and engineering backgrounds outside of biology or medicine who have the potential to integrate their expertise with biomedicine and to develop into productive investigators with a period of mentored study and research.

K30 Clinical Research Curriculum Award (CRCA)—awarded to institutions to stimulate the inclusion of high-quality, multidisciplinary didactic training as part of the career development of clinical investigators. This award supports the development of new didactic programs in clinical research at institutions that do not offer such programs or in institutions with existing programs in clinical research. In the latter, it supports the expansion of programs or improvement in the quality of instruction.

Research and Development-Related Contracts

N01 Research and Development (R&D) Contract—develops or applies new knowledge or tests, screens, or evaluates a product, material, device, or component for use by the scientific community.

Research Program Projects and Centers

P01 Research Program Project—provides a qualified institution, on behalf of a principal investigator, with the support of a broad-based, multidisciplinary, often long-term research program with a particular major objective or theme. A program project involves the organized efforts of groups of investigators who conduct research projects related to the overall program objective. The grant can provide support for the projects and for certain shared resources necessary for the total research effort. Each project supported under a program project grant is expected to contribute to the overall program objective.

P30 Center Core Grant—supports shared resources and facilities for categorical research by a number of investigators

from different disciplines who provide a multidisciplinary approach to a joint research effort or from the same discipline who focus on a common research problem. Although funded independently of the center's component projects or program projects, the core grant relates integratively to them. By providing more accessible resources, this support is expected to ensure greater productivity than that obtained from the separate projects and program projects.

P50 Specialized Center—supports any part of the full range of R&D, from basic to clinical, and may involve ancillary supportive activities, such as protracted patient care necessary to the primary research or R&D effort. The spectrum of activities comprises a multidisciplinary attack on a specific disease entity or biomedical problem area. These grants differ from program project grants in that they are usually developed in response to an announcement of the programmatic needs of an Institute or Division and subsequently receive continuous attention from its staff. Centers also may serve as regional or national resources for special research purposes.

Research Project Grants and Grants Related to Research Projects

R01 Research Project Grant (traditional)—provides support to an institution (domestic or foreign) on behalf of a principal investigator for a discrete project related to the investigator's interests and competence. Most of the research that the NIH supports is maintained through this funding mechanism. Although rare, such a grant may be awarded directly to an individual.

- R03** Small Grant—provides research support specifically limited in time and amount for studies in categorical program areas. Small grants provide flexibility for initiating studies, which are generally for preliminary short-term projects and are nonrenewable.
- R09** Scientific Evaluation—provides the chairman of an initial review group funds for operation of the initial review group.
- R13** Conference Grant—provides funding for conferences to coordinate, exchange, and disseminate information related to program interests. In general, such awards are modest and limited to participation with other organizations in the support of conferences rather than as a provision of sole support. Among the costs eligible for support are salaries, equipment rental, travel, consultant services, and supplies. Prospective applicants should inquire in advance concerning possible interest on the part of an Institute.
- R15** Academic Research Enhancement Award (AREA)—provides support to scientists at eligible domestic institutions for small-scale, new, or expanded health-related research projects, such as pilot research projects and feasibility studies; development, testing, and refinement of research techniques; secondary analysis of available data sets; and similar discrete research projects that demonstrate research capability. This award is directed toward smaller, less-prominent 4-year public and private colleges and universities that provide undergraduate training for a significant number of U.S. research scientists but have not had an adequate share in the growth of the NIH extramural program.
- R18** Research Demonstration and Dissemination Project—provides support to develop, test, and evaluate health-service activities and to foster the application of existing knowledge for the control of categorical diseases.
- R21** Exploratory/Developmental Grant—used by NIAID for bridge awards. The bridge award provides support for a limited time and amount to investigators to enable them to continue meritorious research and improve the competitiveness of future grant applications.
- R24** Resource-Related Research Project—supports research projects that will enhance the capability of resources to serve biomedical research.
- R25** Education Project—provides support to develop or implement a program in education, information, training, technical assistance, coordination, or evaluation.
- R33** Exploratory and Developmental Grants, Phase II—provide a second phase of support for innovative, exploratory, and developmental research begun as an R21 award. Only R21 awardees are eligible to apply for R33 support. Applications are accepted only in response to RFAs and PAs that specify the R33 mechanism.
- R37** Method to Extend Research in Time (MERIT) Award—provides long-term, stable support to investigators who are likely to continue to perform in an outstanding manner and spares them the administrative burdens associated with preparing and submitting research grant applications. An initial 5-year award is accompanied by an opportunity for a 3- to 5-year extension, based on an expedited review of the accomplishments during the initial award period. Investigators may not apply for a MERIT

award. NIH staff and advisors base their selection of MERIT award recipients on competing R01 applications, prepared and submitted in accordance with NIH procedures. MERIT awards are awarded to a limited number of selected investigators who have demonstrated superior competence and outstanding productivity during previous research endeavors.

Small Business Funding Opportunities

- R41** Small Business Technology Transfer Research (STTR) Grant, Phase I—supports cooperative R&D projects between small business concerns and research institutions, limited in time and amount, to establish the technical merit and feasibility of ideas that have potential for commercialization. Awards are made to small business concerns only.
- R42** STTR Grant, Phase II—supports cooperative R&D projects between small business concerns and research institutions, limited in time and amount, to establish the technical merit and feasibility of ideas that have potential for commercialization. Awards are made to small business concerns only.
- R43** Small Business Innovation Research (SBIR) Grant, Phase I—enables small businesses to contribute to the R&D mission of the NIH. Phase I grants support projects, limited in time and amount, to establish the technical merit and feasibility of ideas that ultimately may lead to commercial products or services. The research must be conducted in the United States.
- R44** SBIR Grant, Phase II—enables small businesses to contribute to the R&D mission of the NIH. Phase II grants

support indepth development of ideas whose feasibility has been established in Phase I and that are likely to result in commercial products or services. The research must be conducted in the United States.

Research Training Programs

- T32** Institutional NRSA—enables institutions to grant NRSA for predoctoral and postdoctoral research training in specified shortage areas to individuals selected by the institutions.
- T35** NRSA Short-Term Research Training—provides individuals with research training during off-quarters or summer periods to encourage research careers or research in areas of national need.

Cooperative Agreements

- U01** Research Project (Cooperative Agreement)—provides an assistance relationship between the NIH and a recipient, but with substantial programmatic involvement by the NIH. The NIH assists, supports, or stimulates the recipients and is involved substantially with recipients in conducting projects similar in program content to those for grants, with the NIH playing a “partner” role in the effort.
- U19** Research Program (Cooperative Agreement)—supports a research program of multiple projects directed toward a specific major objective, basic theme, or program goal that requires a broad-based, multidisciplinary, and often long-term approach.
- U24** Resource-Related Research Projects/ Cooperative Agreements—support research projects contributing to

improvement of the capability of resources to serve biomedical research.

U42 Animal (Mammalian and Nonmammalian) Model and Animal and Biomedical Materials Resource Cooperative Agreements (National Center for Research Resources)—develop and support an animal (mammalian and nonmammalian) model or animal or biological materials resources available to all qualified investigators without regard to the scientific disciplines or disease orientations of their research activities or specifically directed to a categorical program. Nonmammalian resources include nonmammalian vertebrates, invertebrates, cell systems, and nonbiological systems.

U54 Specialized Centers Cooperative Agreements—support research and development from basic to clinical, including ancillary supportive activities that create a multidisciplinary focus on a disease or a biomedical problem. Centers also may serve as regional or national resources for special research purposes.

U56 Exploratory Grants Cooperative Agreements—support planning for new programs, expansion or modification of existing resources, and feasibility studies for interdisciplinary programs that may lead to specialized or comprehensive centers.

UC1 NIH Challenge Grants and Partnerships Program, Phase II, Cooperative Agreements (NIAID)—promote joint ventures between the NIH and both domestic and global entities to facilitate rapid biomedical or biotechnology R&D for infectious diseases to benefit public health; projects should have a commercial potential that could not have been attained without matching funds.

Interagency and Intra-Agency Agreements

Y01 NIH Interagency Agreement—provides a written reimbursable agreement by which a component of the NIH provides a source of funds to another Federal organization outside the Department of Health and Human Services (DHHS) to acquire specific products, services, or studies.

Y02 NIH Intra-agency Agreement—provides a written reimbursable agreement by which a component of the NIH provides funds to another NIH component or to another organization within DHHS to acquire specific products, services, or studies.

ACRONYMS

AACTG	Adult AIDS Clinical Trials Group
AADRC	Asthma and Allergic Diseases Research Centers
AAIB	Asthma, Allergy, and Inflammation Branch, DAIT
ACE	Autoimmunity Centers of Excellence
ACERRB	AIDS Clinical and Epidemiology Research Review Branch, DEA
ADAMHA	Alcohol, Drug Abuse, and Mental Health Administration
ADCC	Autoimmune Diseases Coordinating Committee
ADMO	Associate Director for Management and Operations
ADV	adenoviral
AfCS	Alliance for Cellular Signaling
AIDS	acquired immunodeficiency syndrome
AIEDRP	Acute Infection and Early Disease Research Program
AIT	allergen immunotherapy
AMOB	Acquisition Management and Operations Branch, NIAID
APRRB	AIDS Preclinical Research Review Branch, DEA
ARAC	AIDS Research Advisory Committee
AREA	Academic Research Enhancement Award
ART	antiretroviral therapy
ASIR	Richard M. Asofsky Scholars In Research
AVRWG	AIDS Vaccine Research Working Group
BAMBU	Bacteriology and Mycology Biostatistical and Operations Unit
BAMSG	Bacteriology and Mycology Study Group
BIB	Basic Immunology Branch, DAIT
BISC	Bioinformatics Integration Support Contract
BMB	Bacteriology and Mycology Branch, DMID
BRASS	Biomedical Research After School Scholars
BSC	Board of Scientific Counselors
BSE	bovine spongiform encephalopathy
BSL	biosafety level
BSP	Basic Sciences Program, DAIDS
CAB	community advisory board
CAP	community-acquired pneumonia
CASG	Collaborative Antiviral Study Group
CCRB	Complications and Co-Infections Research Branch, DAIDS

CCTPT	Cooperative Clinical Trials in Pediatric Transplantation program
CDA	Confidential Disclosure Agreements
CDC	Centers for Disease Control and Prevention
CEOPP	Community Education and Outreach Partnership Program
CFAR	Centers for AIDS Research
CHAVI	Center for HIV/AIDS Vaccine Immunology
CIB	Clinical Immunology Branch, DAIT
CIPRA	Comprehensive International Program of Research on AIDS
CJD	Creutzfeldt-Jakob disease
CMB	Comparative Medicine Branch, DIR
CMP	Contract Management Program
CMV	cytomegalovirus
CPCRA	Terry Beirn Community Programs for Clinical Research on AIDS
CRADA	Cooperative Research and Development Agreement
CRCA	Clinical Research Curriculum Award
CRMB	Clinical Research Management Branch, DAIDS
CRRB	Clinical Research Resources Branch, DAIDS
CTA	Clinical Trial Agreement
CWD	chronic wasting disease
DAIDS	Division of Acquired Immunodeficiency Syndrome
DAIT	Division of Allergy, Immunology, and Transplantation
DDCSB	Drug Development and Clinical Sciences Branch, DAIDS
DEA	Division of Extramural Activities
DHHS	Department of Health and Human Services
DIR	Division of Intramural Research
DIRB	DAIDS International Research Branch
DMID	Division of Microbiology and Infectious Diseases
DNA	deoxyribonucleic acid
DoD	Department of Defense
DSA	Drug Screening Agreements
EAMB	Extramural Administrative Management Branch, NIAID
EB	Epidemiology Branch, DAIDS
EHDB	Enteric and Hepatic Diseases Branch, DMID
EIR	Employee Invention Reports
ELISA	enzyme-linked immunosorbent assay
ELISPOT	enzyme-linked immunospot

ENSB	Extramural Network Systems Branch, NIAID
ESPRIT	Evaluation of Subcutaneous Proleukin in a Randomized International Trial
FCRDC	Frederick Cancer Research and Development Center
FDA	Food and Drug Administration
FOIA	Freedom of Information Act
FY	fiscal year
GBS	Group B streptococcus
GBV-B	GB virus type B
GBV-C	GB virus type C
GMB	Grants Management Branch, DEA
HAART	HIV highly active antiretroviral therapy
HBV	hepatitis B virus
HCV	hepatitis C virus
HHV	human herpesvirus
HIV	human immunodeficiency virus
HIVRAD	HIV Vaccine Research and Design Program
HIVRB	HIV Research Branch, DAIDS
HLA	human leukocyte antigen
HOPE	Health Omnibus Programs Extension of 1988
HPTN	HIV Prevention Trials Network
HSC	hematopoietic stem cell
HSV	herpes simplex virus
HUD	Department of Housing and Urban Development
HVAD	HIV Vaccine Awareness Day
HVCC	HIV Vaccine Communications Campaign
HVDDT	HIV Vaccine Design and Development Teams
HVTN	HIV Vaccine Trials Network
IAMB	Intramural Administrative Management Branch, NIAID
IAVI	International AIDS Vaccine Initiative
ICs	Institutes and Centers
ICAC	Inner-City Asthma Consortium
ICDs	Institutes, Centers, and Divisions
ICER	International Centers for Excellence in Research
ICIDR	International Collaboration in Infectious Disease Research
ICU	intensive care unit

IDPB	Infectious Disease Pathogenesis Branch, DIR
IHWG	International Histocompatibility Working Group
IL	interleukin
IND	investigational new drug
INRO	Intramural NIAID Research Opportunities
IOM	Institute of Medicine
IPCAVD	Integrated Preclinical/Clinical AIDS Vaccine Development Program
IPCP	Integrated Preclinical/Clinical Program
IPCP-HTM	Integrated Preclinical/Clinical Program for HIV Topical Microbicides
IRB	institutional review board
IRTA	Intramural Research and Training Awardees
ISAAC	International Studies of AIDS-Associated Co-Infections
ITN	Immune Tolerance Network
ITSB	Intramural Technical Systems Branch, NIAID
JDRF	Juvenile Diabetes Research Foundation International
LACD	Laboratory of Advanced Clinical Development, VRC
LAD	Laboratory of Allergic Diseases, DIR
LAM	Laboratory of Animal Medicine, VRC
LCID	Laboratory of Clinical Infectious Diseases, DIR
LCMI	Laboratory of Cellular and Molecular Immunology, DIR
LCT	Laboratory of Clinical Trials, VRC
LHBP	Laboratory of Human Bacterial Pathogenesis, DIR
LHD	Laboratory of Host Defenses, DIR
LI	Laboratory of Immunology
LICP	Laboratory of Intracellular Parasites, DIR
LID	Laboratory of Infectious Diseases, DIR
LIG	Laboratory of Immunogenetics, DIR
LIP	Laboratory of Immunopathology, DIR
LIR	Laboratory of Immunoregulation, DIR
LMI	Laboratory of Molecular Immunology, DIR
LMM	Laboratory of Molecular Microbiology, DIR
LMVR	Laboratory of Malaria and Vector Research, DIR
LPD	Laboratory of Parasitic Diseases, DIR
LPVD	Laboratory of Persistent Viral Diseases, DIR
LV	Laboratory of Virology, VRC
LVD	Laboratory of Viral Diseases, DIR

LVP	Laboratory of Vaccine Production, VRC
LVP	Laboratory of Viral Pathogenesis, VRC
<i>M.tb</i>	<i>Mycobacterium tuberculosis</i>
MACS	Multicenter AIDS Cohort Study
MADGC	Multiple Autoimmune Disease Genetics Consortium
M-CRADA	Materials Cooperative Research and Development Agreement
MDR-TB	multidrug-resistant tuberculosis
MERIT	Method to Extend Research in Time Award
MHC	major histocompatibility complex
MIRB	Microbiology and Immunology Review Branch, DEA
MISB	Management Information Systems Branch, NIAID
MMF	mycophenolate mofetil
MR4	Malaria Research and Reference Reagent Repository
MRI	magnetic resonance imaging
MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
MRU	Microbiology Research Unit
MS	multiple sclerosis
MSG	Mycoses Study Group
MSM	men who have sex with men
MTA	Material Transfer Agreement
MTCT	mother-to-child transmission
MVA	modified vaccinia Ankara
MVDB	Malaria Vaccine Development Branch, DIR
NAAIDC	National Advisory Allergy and Infectious Diseases Council
NARAC	North American Rheumatoid Arthritis Consortium
NARSA	The Network on Antimicrobial Resistance in <i>Staphylococcus aureus</i>
NBL	national biocontainment laboratory
NCRR	National Center for Research Resources
NHLBI	National Heart, Lung, and Blood Institute
NHPCSG	Nonhuman Primate Cooperative Study Group
NIAID	National Institute of Allergy and Infectious Diseases
NIALS	NIAID Immune Assessment Laboratory Service
NICHD	National Institute of Child Health and Human Development
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIEHS	National Institute of Environmental and Health Sciences
NIGMS	National Institute of General Medical Sciences

NIH	National Institutes of Health
NK	natural killer [cells]
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRSA	National Research Service Award
NRTI	nucleoside reverse transcriptase inhibitor
NVP	nevirapine
NVPO	National Vaccine Program Office
OAS	Office of Administrative Services, NIAID
OCA	Office of Clinical Applications, DAIT
OCPL	Office of Communications and Public Liaison, NIAID
OCR	Office of Clinical Research, NIAID
OCRA	Office of Clinical Research Affairs, DMID
OD	Office of the Director, NIAID
OE	Office of Ethics, NIAID
OECT	Office of Epidemiology and Clinical Trials, DAIT
OFM	Office of Financial Management, NIAID
OGA	Office of Global Affairs
OHRM	Office of Human Resources Management, NIAID
OI	opportunistic infections
OKR	Office of Knowledge Resources
OMNI	Office of Management for New Initiatives, NIAID
ONR	Office of Naval Research
OPA	Office of Policy Analysis, NIAID
OPCO	Office of Program Coordination and Operations, DEA
OPCRO	Office for Policy in Clinical Research Operations, DAIDS
OPOSI	Office of Program Operations and Scientific Information, DAIDS
OPOSI	Office of Program Planning, Operations, and Scientific Information, DAIT
ORA	Office of Regulatory Affairs, DMID
OSCPO	Office of Scientific Coordination and Program Operations, DMID
OSPT	Office of Special Populations and Research Training, NIAID
OSRD	Office of Scientific Resource Development
OTD	Office of Technology Development, NIAID
OTIS	Office of Technology Information Systems, NIAID
OTSEP	Office of Training and Special Emphasis Programs
OTT	Office of Technology Transfer, NIH
PA	program announcement

PAB	Pharmaceutical Affairs Branch, DAIDS
PACTG	Pediatric AIDS Clinical Trial Group
PATH	Program for Appropriate Technology in Health
PAVE	Partnership for HIV/AIDS Vaccine Evaluation
PBRB	Pathogenesis and Basic Research Branch, DAIDS
PEG-IFN	pegylated-interferon
PEPFAR	President's Emergency Plan for HIV/AIDS Relief
PFGRC	Pathogen Functional Genomics Resource Center
PGL	phenolic glycolipid
PID	primary immunodeficiency diseases
PIDR	Primary Immunodeficiency Diseases Registry
PIPB	Parasitology and International Programs Branch, DMID
PMB	Pediatric Medicine Branch, DAIDS
PR	protease
PRDB	Preclinical Research and Development Branch, DAIDS
PRP	polyribosylribose phosphate
PrP	prion protein
PSB	Prevention Sciences Branch, DAIDS
RAB	Regulatory Affairs Branch, DAIDS
RBL	Regional Biocontainment Laboratories
RCE	Research Centers of Excellence
RCMI	Research Centers in Minority Institutions
R&D	research and development
RDB	Respiratory Diseases Branch, DMID
RFA	request for applications
RFP	request for proposals
RML	Rocky Mountain Laboratories
RMVB	Rocky Mountain Veterinary Branch, DIR
RNA	ribonucleic acid
RPAB	Referral and Program Analysis Branch, DEA
RSUM	Research Supplements for Underrepresented Minorities
RSV	respiratory syncytial virus
RT	reverse transcriptase
RTB	Research Technologies Branch, DIR
SARS	severe acute respiratory syndrome
SARS-CoV	SARS-associated coronavirus

SBIR	Small Business Innovation Research
SLE	systemic lupus erythematosus
SMART	Strategies for Management of Anti-Retroviral Therapy
SNP	single nucleotide polymorphism
SPR	Summer Policy Retreat
SRB	Special Review Branch, DEA
SRP	Scientific Review Program, DEA
STD	sexually transmitted diseases
STI	sexually transmitted infections
STIB	Sexually Transmitted Infections Branch, DMID
STI CTG	Sexually Transmitted Infections Clinical Trials Group
STTR	Small Business Technology Transfer
TAACF	Tuberculosis Antimicrobial Acquisition and Coordinating Facility
TB	tuberculosis
TBRU	Tuberculosis Research Unit
TDRU	Tropical Diseases Research Unit
TEAC	Technology Evaluation Advisory Committee
TIB	Targeted Interventions Branch, DAIDS
TIB	Transplantation Immunobiology Branch, DAIT
TIGR	The Institute for Genomic Research
TMP-SMX	trimethoprim-sulfamethoxazole
TMRC	Tropical Medicine Research Centers
TRP	Therapeutics Research Program, DAIDS
TSE	transmissible spongiform encephalopathy
USAID	U.S. Agency for International Development
USAMRIID	U.S. Army Medical Research Institute of Infectious Diseases
USAMRMC	U.S. Army Medical Research and Materiel Command
USIDNET	U.S. Immunodeficiency Network
USJCMSP	U.S.–Japan Cooperative Medical Science Program
VA	Veterans Administration
VB	Virology Branch, DMID
VCRB	Vaccine Clinical Research Branch, DAIDS
VDRG	Vaccine Developmental Resources Group
Vif	Virion Infectivity Factor
VPP	Vaccine Pilot Plant

VPRP	Vaccine and Prevention Research Program, DAIDS
VRC	Vaccine Research Center
VRE	vancomycin-resistant enterococci
VZV	varicella-zoster virus
WG	Wegener's granulomatosis
WHO	World Health Organization
WIHS	Women's Interagency HIV Study
WITS	Women and Infants Transmission Study
WNV	West Nile virus
WPR	Winter Program Review

INDEX

A

Academic Research Enhancement Award (AREA) 179, 182

Acambis, Inc. 77

Acquired Immunodeficiency Syndrome (AIDS) i-iii, v, 5-7, 9, 11-16, 24, 26, 28, 30-31, 33, 35-36, 38-44, 46, 64-66, 72, 75, 78, 90-93, 95, 104-108, 111-112, 114, 116, 119, 121, 123, 126-128, 134-136, 141, 143-146, 148-153, 164-165, 167, 170, 182

Acquired Immunodeficiency Syndrome Research Review Committee 148

Acquisition Management and Operations Branch (AMOB), NIAID 182, 201

Acute HIV Infection and Early Disease Research Program (AIEDRP) 91, 182

Adenoviral Vectors (ADV) 34, 36, 59, 175, 182

Adult AIDS Clinical Trials Group (AACTG) 12, 16, 35, 42, 66, 106-107, 134, 182

Aedes aegypti 85, 89

agreements 4, 37, 78, 80, 92, 145, 148, 156, 171

AIDS. *See* acquired immunodeficiency syndrome

AIDS Clinical and Epidemiology Research Review Branch (ACERRB), DEA 182, 205

AIDS Preclinical Research Review Branch (APRRB), DEA 182, 205

AIDS Research Advisory Committee 14, 38, 128, 150

AIDS Research and Reference Reagent Program 12, 16, 75, 95, 136

AIDS Vaccine Research Working Group (AVRWG) 14, 128, 152, 182

Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA) 164, 182

allergen immunotherapy (AIT) 51

allergy ii, 5, 26-27, 49-51, 98, 112, 141, 154

Allergy, Immunology, and Transplantation Research Committee 154

Alliance for Cellular Signaling (AfCS) 62, 182

Animal (Mammalian and Nonmammalian) Model and Animal and Biomedical Materials Resource Cooperative Agreements 181

anthrax 9, 22, 54, 56, 58-60, 71-73, 83-84, 89-90, 136, 173

Antimicrobial Drug Resistance 23, 141

antiretroviral therapy (ART) 12-13, 39, 41, 43, 64-65, 91, 105-106, 119, 141, 182

antiviral agents 67, 81, 139

arbovirus 139

arthritis i-ii, 18, 53, 64, 69, 86, 88, 98, 137, 171

Arthritis Foundation 53, 88, 137

ASIR. *See* Richard M. Asofsky Scholars in Research

Aspergillus fumigatus 83, 85, 89, 182

Associate Director for Management and Operations (ADMO) 160, 182, 201

asthma i-iii, 17-18, 26-27, 49-51, 69-70, 86-87, 97, 103-104, 141-142

Asthma and Allergic Diseases Research Centers (AADRC) 17, 20, 50

atopic dermatitis 51, 54

autoimmune diseases iii, 9, 17-18, 27, 52-53, 69-70, 87-88, 97, 103-104, 120, 124, 133, 137

Autoimmune Diseases Coordinating Committee (ADCC) 52, 104, 182

Autoimmunity Centers of Excellence (ACE) 18, 20, 52, 69, 88, 99, 104, 182

Aviron 80, 175

awards v, 10, 19, 26, 37-38, 42, 56-57, 73, 88, 91-92, 101, 108, 112, 116, 145, 168, 171, 179-180

azithromycin 68, 109

B

bacterial vaginosis 114

bacteriology 21, 156

Bacteriology and Mycology Biostatistical and Operations Unit (BAMBU) 68, 182

Bacteriology and Mycology Branch (BMB), DMID 182

Bacteriology and Mycology Study Group (BAMSG) 46, 68, 91, 182

Basic Immunology Branch (BIB), DAIT 182, 204

Basic Sciences Program (BSP), DAIDS 11, 182, 202

bilateral programs 92

Biodefense and Emerging Infections Research Resources Program 72

Biodefense Research Agenda for CDC Category A Agents i, 9

biodiversity 93

bioengineering 61

biofilms 47

bioinformatics 4, 22, 31, 56-57, 61, 63, 86-87, 140

Bioinformatics Integration Support Contract (BISC) 63, 182
 Biology of the Microbe 58
 Biomedical Research After School Scholars (BRASS) 6, 182
 biosafety level (BSL) 27, 72, 182
 Biotechnology Engagement Program 93
 Board of Scientific Counselors (BSC), NIAID 29, 38, 158, 182
 borreliosis 73, 78-79
 bovine spongiform encephalopathy or "mad cow" disease (BSE) 26, 81, 182
 breastfeeding 14, 41, 106
Brucella suis 55, 84
Brugia malayi 89
 bubonic plague 58, 141
 budget iii, 3-4, 8, 10, 37-38, 92, 158, 164-165, 172
 BufferGel® 116-117
Burkholderia mallei 55, 58, 74, 84-85, 89
Burkholderia pseudomallei 58, 74, 85, 89
Burkholderia thailandensis 89

C

canarypox 127
 capsid 40
 carcinogenesis 92
 Career Development Award 177
 Career Transition Award 177
 Category A, B, and C agents 22, 55, 72, 85
 CD25 174
 CD4+ T cells 43-44
 Center Core Grant 178
 Centers for AIDS Research (CFAR) 12, 16, 92, 108, 183
 Centers for Disease Control and Prevention (CDC) i, 9, 15, 41, 47, 52, 54, 67, 73-74, 76, 78, 80, 104, 111, 121, 128, 130-131, 134, 141-143, 147, 151, 153, 164, 183
 Center for HIV/AIDS Vaccine Immunology (CHAVI) 128, 183
 Chagas disease 89
 chlamydia 24, 62, 83, 108, 114-115, 126, 129
 chronic fatigue syndrome 170
 chronic wasting disease (CWD) 26, 81-82, 183
 cidofovir 57
 CIPRA. *See* Comprehensive International Program of Research on AIDS
 Civilian Research and Development Foundation 93
 Clinical Immunology Branch (CIB), DAIT 183, 204
 Clinical Investigator Award 177
 Clinical Research Curriculum Award (CRCA) 178, 183
 Clinical Research Management Branch (CRMB), DAIDS 183, 203
 Clinical Research Resources Branch (CRRB), DAIDS 183, 203
 clinical studies 12, 80
 clinical trials 6-7, 12-14, 18-19, 21-23, 30-36, 42-43, 52-53, 59, 66, 68-69, 77, 80, 87-88, 91, 98, 100-101, 103-104, 106-107, 111, 114-118, 121-123, 127-130, 132, 134-135
 Clinical Trial Agreement (CTA) 172, 183
Clostridium botulinum 73, 85
Clostridium perfringens 55, 74, 84, 89
Coccidioides immitis 73, 89
 Collaborative Antiviral Study Group (CASG) 46, 57, 68, 76, 182
 Committee Management Office 38
 community-acquired pneumonia (CAP) 47, 67-68, 182
 Community Advisory Board (CAB) 15, 182
 Community Education and Outreach Partnership Program (CEOPP) 7, 108, 183
 Community Programs for Clinical Research on AIDS 12, 16, 42, 66, 107, 170, 183
 Comparative Medicine Branch (CMB) 183, 205
 Complications and Co-Infections Research Branch (CCRB), DAIDS 182, 203
 Comprehensive International Program of Research on AIDS (CIPRA) 14, 42, 92, 123, 183
 computer linkages 27
 Conference Grant 179
 Confidential Disclosure Agreements (CDA) 172, 183
 Contract Management Program (CMP) 37, 183
 Cooperative Agreement 180-181
 Cooperative Centers for Translational Research on Human Immunology and Biodefense 20, 55, 132
 Cooperative Clinical Trials in Pediatric Transplantation (CCTPT) 118, 183
 Cooperative Research and Development Agreement (CRADA) 4, 34, 70, 80, 135, 172-173, 183, 186

Cooperative Research for the Development of Vaccines, Adjuvants, Therapeutics, Immunotherapeutics, and Diagnostics for Biodefense 56

coronavirus 34, 67, 71, 74-77, 85, 135, 139, 142, 189

Coxiella burnetii 55, 74, 84

CPCRA. *See* Terry Beirn Community Programs for Clinical Research on AIDS

Creutzfeldt-Jakob disease (CJD) 81, 183

Crohn's disease 70, 142, 175

Crucell 174

Cryptococcus neoformans 83, 89

Cryptosporidium parvum 55, 66, 74, 83-84, 89

Culex pipens 89

cytokine 33, 70, 86, 174

cytomegalovirus (CMV) 21, 33, 67, 126, 129, 139, 183

cytotoxic T lymphocytes 14, 40

D

Dale and Betty Bumpers Vaccine Research Center (VRC) 6, 30-36, 59, 90-91, 112, 126, 128, 134-135, 165, 173, 185-186, 190, 193, 199, 202, 206-207

databases 24-25, 56, 62-64, 66, 83, 85-87, 100

dengue i, 28, 33, 71-72, 77, 126, 133, 139

deoxyribonucleic acid (DNA) 24, 26, 33-35, 40, 44, 47, 50, 55, 59, 64, 70, 75, 77, 83, 87, 91, 124, 127, 130-131, 134-137, 140, 173-176, 183

Department of Defense (DoD) 15, 22, 41, 54, 62, 128, 183

Department of Energy 84

Department of Health and Human Services (DHHS) 1, 3-4, 8, 22, 92-93, 122, 126, 147, 163-164, 170, 181, 183

diabetes i, iii, 52-53, 64, 69, 86-87, 98, 118, 164

diagnostic tools 21, 67-68, 72, 125

diarrheal diseases 46

directors 15, 29, 52, 94, 128, 148, 163, 171

Division of Acquired Immunodeficiency Syndrome (DAIDS), NIAID 11, 37, 64-69, 91, 107, 115, 122-123, 126-129, 134, 136, 150, 161, 183, 202-203

Division of Allergy, Immunology, and Transplantation (DAIT), NIAID 17-18, 37, 49, 52-53, 63, 68-69, 86-87, 97-99, 118-120, 123-124, 126, 131-132, 137, 161, 176, 182-183, 187, 189, 203

Division of Computer Research and Technology 27

Division of Extramural Activities (DEA), NIAID 37, 182-184, 186-189, 204

Division of Intramural Research (DIR), NIAID 26-29, 31, 43, 47-48, 58-60, 70, 75, 81, 90, 95, 100, 112-113, 124-126, 133-134, 137, 158-160, 173, 175, 183, 185-186, 188, 205

Division of Microbiology and Infectious Diseases (DMID), NIAID 21-25, 30-31, 34, 36-37, 66-68, 77, 81, 83, 115-116, 121-122, 126, 129-131, 133, 138, 160-161, 175-176, 182-183, 187-189, 204

DNA. *See* deoxyribonucleic acid

DnaE2 141

Drug Development and Clinical Sciences Branch (DDCSB), DAIDS 183, 203

drug discovery 12, 21, 27, 44, 64-67, 123-124

drug resistance 21, 23, 28, 42-43, 45-47, 65, 78, 95, 100, 124, 141

Drug Screening Agreements (DSA) 172, 183

E

E25 anti-IgE 176

ebola virus 174

Education Project 179

Ehrlichia spp 89

Ehrlichiosis 73, 79, 89

emerging and re-emerging infectious diseases 22, 74

Emerging Viral Diseases Centers 77

Employee Invention Reports (EIR) 172, 183

end-stage renal disease 118

Entamoeba histolytica 55, 74, 83-84, 89

enteric 55, 73, 92, 141, 183

enterococci 45, 141, 190

Environmental Protection Agency 50

enzyme-linked immunosorbent assay (ELISA) 79, 184

enzyme-linked immunospot (ELISPOT) 87, 98, 184

Escherichia coli 55, 84, 89

Evaluation of Subcutaneous Proleukin in a Randomized International Trial (ESPRIT) 42, 184

Expert Panel on Atopic Dermatitis and Vaccinia Immunization 54

Expert Panel on Immunity and Biodefense 54

Exploratory and Developmental Grants 179

Exploratory Grants Cooperative Agreements 181

F

Fauci, Anthony S. iii, v, 145, 160

filariasis 138

fiscal year (FY) 10, 14, 18-19, 46, 50-52, 56-57, 66-69, 72, 75, 77, 79, 85-86, 88-93, 99, 103, 108-113, 115, 118-119, 122, 128, 132, 137, 163-168, 171-174, 184

flaviviruses 28, 77

FluMist 23, 80, 133

Fogarty International Center 1, 4, 126

food allergy 49

Food and Drug Administration (FDA) 1, 23, 34, 36, 47, 52, 66-67, 72, 75, 80, 121-122, 130, 153, 184

Francisella tularensis 73, 85, 89

Frederick Cancer Research and Development Center (FCRDC) 27, 184

Freedom of Information Act (FOIA) 4, 184

G

gas gangrene 89

genomics 20, 23-24, 56, 76, 83, 85-86, 110, 119, 122, 140, 188

Giardia lamblia 55, 74, 84, 89

GlaxoSmithKline 24, 68, 109, 115, 124, 175

Global Alliance for Vaccines and Immunization 93, 130

global health v, 9, 22-24, 67, 71-72, 78, 90, 138, 152

Global Health Research Plan for HIV/AIDS, Malaria, and Tuberculosis 9, 71, 78, 90

glycoprotein 34, 135

gonorrhea 23-24, 83, 108, 114, 129

gp120 32-34

graft rejection 19, 70, 86-88, 104, 110, 118-119

grants iii, 11, 13, 22-24, 37-39, 46, 56, 65, 68-69, 72, 75, 78-80, 92, 99, 112, 114, 121, 123, 126, 145, 148, 154, 156, 171, 178-180

Grants Management Branch (GMB) 37, 184, 205

Group B Streptococcus (GBS) 89, 109, 184

H

HAART. *See* highly active antiretroviral therapy

health disparities 9, 103, 108, 143

Health Omnibus Programs Extension (HOPE) 150, 170, 184

hematopoietic stem cell 53, 104, 110, 120, 184

hemorrhagic fevers 67, 73, 139

hepatitis A ii, 74

hepatitis B virus (HBV) 43, 184

Hepatitis C Cooperative Research Centers 95, 104

hepatitis C virus (HCV) 9, 42-43, 73, 94-96, 104, 142-143, 175, 184

hepatitis E virus 73, 133

herpes simplex virus (HSV) 109, 173, 184

Herpevac Trial for Women 109, 115

highly active antiretroviral therapy (HAART) 12, 39, 42-44, 64, 105-106, 119, 184

histocompatibility 61, 88, 110, 120, 124, 132, 137, 186

Histoplasma capsulatum 89

HIV/AIDS ii-iii, 6-7, 9, 11, 13-15, 24, 30, 39-42, 44, 64-65, 72, 78, 90-92, 104-105, 107-108, 114, 123, 127-128, 135, 143, 164-165, 183, 188

HIV Prevention Trials Network (HPTN) 14, 16, 41, 91, 106, 116-117, 184

HIV Vaccine Design and Development Teams (HVDDT) 14, 16, 127, 184

HIV Vaccine Developmental Resources Contracts 16

HIV Vaccine Research and Design Program (HIVRAD) 13, 16, 127, 184

HIV Vaccine Trials Network (HVTN) 6, 13, 16, 35, 41, 91, 106, 127-129, 134, 136, 152, 184

human immunodeficiency virus (HIV) i, 9, 11, 39, 184

human leukocyte antigen (HLA) 14, 53, 88, 110, 120, 124, 132, 184

human papillomavirus 105-106

Human Resources Operations Branch C 4

I

immune-based therapies 18, 50, 57, 69, 87

immune response ii, 12-13, 24, 27-28, 31-33, 35-36, 51, 53, 55, 58-59, 61-62, 74-75, 80, 86, 88, 95, 119-120, 124, 130-131, 133-134, 173

immune system i-ii, 11-13, 17-19, 26-27, 30, 32-33, 39-40, 42-43, 47, 50, 52, 54, 61, 64-65, 69-71, 86-88, 97-98, 103, 118-120, 123-124, 126, 128, 132, 141

immune tolerance 53, 69, 86-87, 97-99, 118-119

Immune Tolerance Network (ITN) iii, 18, 20, 50, 52, 69, 85, 87, 89, 97, 104, 119, 185

immunogenetics 87, 154

immunomodulation trials 20, 132

immunostimulants 56

immunotherapy 51, 75, 98, 182

Independent Scientist Award 177

infectious diseases i, iii, v, 9, 21-22, 24-28, 45, 54-57, 63-64, 66, 68, 70-73, 83-85, 90-93, 112, 120, 124, 126, 130-132, 137, 140, 145, 156, 181

influenza i-ii, 6, 21-23, 28, 64, 67, 71-75, 79-81, 85, 89, 129-131, 133, 139, 142
 influenza viruses 79-80
 Inner-City Asthma Consortium (ICAC) 18, 20, 50, 184
 Inner-City Asthma Study iii, 49, 50, 103
 innovation grants 13
 Innovation Grants for AIDS Research Program 11, 44, 65, 116
 Institutes, Centers, and Divisions (ICDs) 29, 164, 184
 Institutes and Centers (ICs) 52, 90, 94, 120, 164, 167, 184
 Institute of Medicine (IOM) 8, 129, 185
 Institutional NRSA 180
 insulin 65, 86, 98
 Integrated Preclinical/Clinical AIDS Vaccine Development (IPCAVD) Program 13, 16, 127, 185
 Integrated Preclinical/Clinical Program (IPCP) 12, 16, 44, 65, 116, 185
 Integrated Preclinical/Clinical Program for HIV Topical Microbicides (IPCP-HTM) 116, 185
 intensive care units 45
 Interagency Task Force on Antimicrobial Resistance 47
 interferon 43, 76, 94, 104, 139, 188
 interleukin-2 44, 141
 interleukin-4 86
 international agencies and organizations 93
 International Centers for Excellence in Research (ICER) 90, 184
 International Centers for Infectious Diseases Research 68
 International Centers for Tropical Diseases Research 102
 International Collaboration in Infectious Disease Research (ICIDR) 91, 185
 International Cooperative Biodiversity Groups Program 93
 International Histocompatibility Working Group (IHWG) 53, 88, 120, 185
 International Studies of AIDS-Associated Co-Infections Program (ISAAC) 44, 65, 186
 International Studies of AIDS-Associated Co-infections Program (INRO) 123, 185
 Intramural NIAID Research Opportunities 112, 185
 Intramural NRSA Individual Postdoctoral Program 177

Intramural Research and Training Awardees (IRTA) 112-113, 185
 Intramural Research Programs 58
 Intramural Research Training and Collaborative Research 90
 investigational new drug (IND) 34, 185
Ixodes scapularis 85, 89

J

Japan 90, 92, 102, 189
 Japanese encephalitis virus 60, 74
 Jordan Report 23
 Juvenile Diabetes Research Foundation International (JDRF) 50, 52, 69, 87, 97, 104, 119, 185

K

kidney iii, 19, 62, 69, 87, 98, 110, 118-119, 143
 Kyasanur forest virus 74

L

laboratories 5, 26-27, 53, 57-58, 70, 81, 88, 90, 98, 100, 102-103, 112, 120, 130, 139, 158, 172, 188
 Laboratory of Advanced Clinical Development (LACD), VRC 182, 202
 Laboratory of Allergic Diseases (LAD), DIR 2, 185, 205
 Laboratory of Animal Medicine (LAM), VRC 2, 185, 202
 Laboratory of Cellular and Molecular Immunology (LCMI), DIR 2, 185, 205
 Laboratory of Clinical Infectious Diseases (LCID), DIR 2, 185, 205
 Laboratory of Clinical Trials (LCT), VRC 2, 185, 202
 Laboratory of Host Defenses (LHD), DIR 2, 173, 175, 185, 205
 Laboratory of Human Bacterial Pathogenesis (LHBP), DIR 2, 185, 205
 Laboratory of Immunogenetics (LIG), DIR 2, 174-175, 185, 205
 Laboratory of Immunology (LI) 2, 174, 202, 205
 Laboratory of Immunopathology (LIP), DIR 2, 185, 206
 Laboratory of Immunoregulation (LIR), DIR 2, 174, 185, 206
 Laboratory of Infectious Diseases (LID), DIR 2, 173-174, 185, 206

Laboratory of Intracellular Parasites (LICP), DIR 2, 174, 185, 206
Laboratory of Malaria and Vector Research (LMVR), DIR 185, 206
Laboratory of Molecular Immunology (LMI), DIR 185, 206
Laboratory of Molecular Microbiology (LMM), DIR 2, 176, 185, 206
Laboratory of Parasitic Diseases 2, 185, 195, 206
Laboratory of Persistent Viral Diseases (LPVD), DIR 2, 206
Laboratory of Vaccine Production (LVP), VRC 2, 202
Laboratory of Viral Diseases (LVD), DIR 2, 173, 176, 206
Laboratory of Viral Pathogenesis (LVP), VRC 2, 151, 202
Laboratory of Virology (LV), VRC 2, 202
Laboratory Review Process, DIR 28-29
lactobacillus 176
Large-Scale Antibody and T Cell Epitope Discovery Program 133
Lassa virus 9, 36, 59, 135
La Montagne, John R. v
Legionella pneumophila 89
Legionnaire's disease 89
legislative chronology 170
leishmaniasis 89
Leishmania major 89
leprosy 93, 138
licensure 23, 35, 36, 72, 114
Liver and Pancreatic Disease in HIV Infection Program 44, 65-66
Lyme Disease 5, 78, 89

M

M.tb 66, 72, 78, 111, 121-124, 138, 186
"mad cow" disease. *See* bovine spongiform encephalopathy
magnetic resonance imaging (MRI) 62, 186
major histocompatibility complex (MHC) 61, 63, 124, 132, 137, 186
malaria i-ii, 21, 23-24, 26, 28, 45-46, 62, 65-67, 71, 83-85, 89-91, 100-102, 111, 121, 124, 126, 129, 132, 134, 138, 141, 164
Malaria Research and Reference Reagent Resource (MR4) 85, 101
Malaria Research and Training Center 27

Malaria Vaccine Development Branch (MVDB) 100, 133, 186, 206
malignancies 64-66, 105, 119
Marburg virus 9
mast cells 27, 86
Materials Cooperative Research and Development Agreement (M-CRADA) 172, 186
Material Transfer Agreement (MTA) 172, 186
Maxygen 175
men who have sex with men (MSM) 6-7, 41-42, 105, 107-108, 115, 186
Mentored Patient-Oriented Research Career Development Award 177
Mentored Quantitative Research Career Development Award 177
merozoite surface protein 176
methicillin-resistant *Staphylococcus aureus* (MRSA) 45, 141, 186
Method to Extend Research in Time (MERIT) Award 179-180, 186
MHC tetramer core facility 137
microbes i-ii, 9, 21-26, 54-56, 61, 83, 109, 114, 140
microbicides 11, 14, 42, 68, 106, 109-110, 114-117
Microbiology and Infectious Diseases Research Committee 156-157
Microbiology Research Unit (MRU) 186
Microchip drug delivery system 62
Midcareer Investigator Award in Patient-Oriented Research 177
minority health 1, 103
Minority Researchers' Training Program 111
modified vaccinia Ankara (MVA) 36, 40, 56, 58-59, 127, 134, 142, 186
monkeypox 22, 59, 71, 142
mother-to-child transmission (MTCT) ii, 13-14, 41-43, 106, 186
Multicenter AIDS Cohort Study (MACS) 11, 16, 39, 105, 136, 186
Multidrug-resistant tuberculosis (MDR-TB) 46, 58, 74, 186
Multilateral Initiative on Malaria v, 93, 102, 130, 138
Multiple Autoimmune Disease Genetics Consortium (MADGC) 53, 88, 137, 186
multiple sclerosis (MS) iii, 53, 64, 69, 98, 104, 186
musculoskeletal and skin diseases 53, 88, 137, 171
Mycobacterium smegmatis 85, 89, 122
Mycobacterium tuberculosis (M.tb). *See* *M.tb*

Mycology 21, 46, 68, 91, 156, 182
mycophenolate mofetil (MMF) 70, 186
Mycoses Study Group (MSG) 68, 186

N

National Academy of Sciences 26, 129
National Advisory Allergy and Infectious Diseases Council (NAAIDC), NIAID 8, 29, 37, 92, 145, 158, 186
National Biocontainment Laboratory (NBL) 22, 72, 186
National Cancer Institute 1, 62, 66, 124, 133
National Center for Research Resources (NCRR) 108, 164, 181, 186
National Center on Minority Health and Health Disparities 1
National Heart, Lung, and Blood Institute (NHLBI) iii, 1, 50, 69, 118, 186
National Institute of Allergy and Infectious Diseases (NIAID) i-iii, v, 1-6, 8-10, 12-15, 18-19, 21-27, 29-31, 33, 34, 37-44, 46-59, 61-65, 67-68, 70-86, 88-97, 100-133, 136-141, 143-145, 147-150, 152, 154-160, 163, 165-168, 170-174, 177, 179, 181-187
National Institute of Arthritis and Musculoskeletal and Skin Diseases 1, 53, 88, 137, 171
National Institute of Child Health and Human Development (NICHD) 1, 14, 19, 88, 186
National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) 1, 50, 52, 63, 65-66, 69, 87, 95, 97-98, 104, 110, 118-119, 186
National Institute of Environmental and Health Sciences (NIEHS) 1, 49-50, 131, 164, 187
National Institute of General Medical Sciences (NIGMS) 1, 62, 86, 187
National Institute on Drug Abuse 1, 14, 65
National Institutes of Health (NIH) i, iii, v, 1, 3-6, 8, 12, 19, 22, 26-27, 29, 35-36, 38, 52-53, 56-57, 59, 63, 67, 70, 72, 75, 79, 81-82, 90, 92, 94-95, 100, 103-104, 111, 113, 120-121, 128, 134, 136, 142-145, 147-149, 151-152, 154, 156-161, 163-165, 167-168, 170-173, 177-181, 187-188
National Research Service Award (NRSA) 177, 180, 187
National Vaccine Program Office (NVPO) 130, 187
natural killer (NK) cells 44, 187
Nematode species 89
Network on Antimicrobial Resistance in *Staphylococcus aureus* (NARSA) 46, 140, 186

neurosyphilis 114
neutrophil 58
nevirapine (NVP) 43, 106, 187
new drugs and therapeutic agents 12
North American Rheumatoid Arthritis Consortium (NARAC) 53, 88, 137, 186
nosocomial infections 21, 45
NRSA for Senior Fellows 177

O

Office of Administrative Services (OAS), NIAID 3, 160, 187, 201
Office of Biodefense Research, NIAID 161
Office of Clinical Research (OCR), NIAID 3, 160, 187, 201
Office of Communications and Public Liaison (OCPL), NIAID 3, 5-6, 160, 187, 201
Office of Ethics (OE), NIAID 3, 160, 187
Office of Financial Management (OFM), NIAID 3, 161, 187, 201
Office of Global Affairs (OGA), NIAID 4, 161, 187, 201
Office of Human Resources Management (OHRM), NIAID 187, 201
Office of Management for New Initiatives (OMNI), NIAID 4, 160, 187, 201
Office of Naval Research (ONR) 84, 187
Office of Policy Analysis (OPA), NIAID 4, 161, 187, 202
Office of Special Populations and Research Training (OSPRT), NIAID 38, 103, 187, 205
Office of Technology Development (OTD), NIAID 4, 161, 172-173, 187, 202
Office of Technology Information Systems (OTIS) 4, 161, 187, 202
Office of Technology Transfer (OTT), NIH 172, 188
Office of the Director (OD), NIAID 3, 37, 160-161, 187, 201
Office of Training and Special Emphasis Programs (OTSEP) 112, 187
opportunistic infections (OI) 12, 39, 42, 64-65, 105, 108, 148, 187
organ transplantation iii, 69, 118
outreach activities 5, 14, 103, 106, 112

P

pancreatic disease 44, 65-66
 Pandemic Preparedness in Asia 75, 80
 parainfluenza 28, 67, 133, 139
 parasites ii, 21, 26, 28, 45-46, 62, 67, 83, 100, 138
 Partnership for HIV/AIDS Vaccine Evaluation (PAVE) 15, 41, 128, 188
 Pathogen Functional Genomics Resource Center (PFGRC) 56, 76, 85, 122, 140, 188
 pathogen genomics 24
 Pediatric AIDS Clinical Trials Group (PACTG) 12, 16, 66, 106-107
 pelvic inflammatory disease (PID) 24, 108
 pertussis vaccine v, 92
 PfEMP1 175
 plague 9, 26, 28, 56, 58, 83, 89, 141
 planning 3-4, 8-9, 14, 36, 38, 41, 72, 108, 117, 143-144, 181
Plasmodium falciparum 83, 100, 134, 144
Plasmodium vivax 89
 Pneumococcal Reference Laboratory 139
 pneumococcus 130
Pneumocystis carinii 66, 89
 pneumonia ii, 21, 23, 39, 45, 47, 66-68, 74, 79, 89, 130, 182
 policy retreats 8
 polymerase chain reaction (PCR) 59, 75
 polyribosylribose phosphate (PRP) 139, 188
 Postdoctoral Individual NRSA 177
 poxvirus 36, 58, 67, 134
 Predoctoral Individual National Research Service Award (NRSA) 177
 Prevention Research 11, 13, 41, 153
 Primary Immunodeficiency Diseases Registry (PIDR) 88, 137, 188
 primates 31, 33-34, 59, 81, 116, 129, 134
 prion diseases 26, 28, 73, 81
 prion protein (PrP) 81, 188
 PRO 2000/5 gel 116-117
Profile iii
 program announcement (PA) 63, 107, 176, 188
 program reviews 8
 Project EXPLORE 41-42
 protease (PR) 13, 42, 64, 94, 188
 protease inhibitors 13, 42

Protein Zinc Finger Domains 174
 proteins 11, 21, 24, 26, 32-34, 39, 55-56, 58-59, 61-65, 72, 74, 76, 81, 84, 86, 110, 123-124, 127, 132, 135, 140, 173-174
 proteomics 25, 58, 61
 Public Health Action Plan to Combat Antimicrobial Resistance 23, 47, 67

R

re-emerging diseases i, 22, 71
 Reagents and Reference Standards 139
 references 141
 Referral and Program Analysis Branch (RPAB), DEA 37, 188
 Regional Biocontainment Laboratories (RBL) 22, 72, 188
 repositories 123, 136, 138
 request for applications (RFA) 37, 92, 179, 188
 Research Agenda for Emerging Infectious Diseases 71
 research and development (R&D) ii, 4, 13, 15, 32, 36-37, 40, 63, 68, 72, 80, 95, 116, 126, 128, 130, 133, 166, 172-173, 178, 180-181, 188
 Research Centers in Minority Institutions (RCMI) 108, 188
 Research Centers of Excellence (RCE) 22, 72, 188
 Research Demonstration and Dissemination Project 179
 Research Program Project 178
 Research Project Grant 178
 Research Supplements for Underrepresented Minorities (RSUM) 108, 112, 188
 Resource-Related Research Project 179
 Resource-Related Research Projects/Cooperative Agreements 180
 respiratory syncytial virus (RSV) 28, 67, 129, 188
 reverse transcriptase (RT) 13, 42-43, 64, 187-188
 ribonucleic acid (RNA) 43-44, 64, 75, 188
 Richard M. Asofsky Scholars In Research (ASIR) 111-112, 182
Rickettsia rickettsii 89
Rickettsia typhi 55, 84, 89
 Rift Valley fever 73
 Rocky Mountain Laboratories (RML) 2, 5, 27, 79, 81-82, 205-206
 Rocky Mountain spotted fever 89

S

Salmonella 46, 55, 74, 84-85, 89, 141
Salmonella typhi 89
 SARS. *See* severe acute respiratory syndrome
 SARS-associated coronavirus (SARS-CoV) 74-76, 189
Schistosoma mansoni 89
 schistosomiasis 70, 138-139, 142, 175
 Science Applications International Corporation 101
 Scientific Evaluation 179
 Scientific Review Program (SRP) 37, 189
 scleroderma 53, 103-104
 scrapie 81
 screening program 67, 139
 severe acute respiratory syndrome (SARS) i, 22-23, 28, 31, 34, 55-56, 60, 71, 73-77, 85, 129-130, 133, 135-136, 139, 142, 173-175, 189
 severe combined immunodeficiency disease 137
 sexually transmitted diseases (STDs) 9, 14, 41, 68, 110, 114, 143-144, 189
 sexually transmitted infections (STIs) 5, 21, 24, 42, 66, 68, 108-110, 114-115, 171, 189
 Shigella 46, 55, 74, 84-85
 Simian Vaccine Evaluation Units 16, 129, 136
 single nucleotide polymorphisms (SNP) 53, 120, 189
 Sjögren's syndrome 104
 skin diseases 1, 53, 88, 137, 171
 Small Business Biodefense Program 56
 Small Business Innovation Research (SBIR) 38, 65, 101, 115, 123, 180, 189
 Small Business Technology Transfer (STTR) 38, 180, 189
 small grant 179
 smallpox 9, 22, 28, 30-31, 36, 54-60, 67, 71, 73, 126, 132, 134-135, 142, 173
 specialized center 178
 St. Louis encephalitis virus 28
 Staphylococcus 23, 45-47, 55, 67, 73, 84-85, 140-141, 186
 STD Clinical Trials Unit 68, 109, 114-115
 STD Cooperative Research Centers 114
 STD Prevention Primate Unit 115
 strategic planning v, 8-9
 Strategic Plan for Addressing Health Disparities 9, 103

Strategies for Management of Anti-Retroviral Therapy (SMART) 42, 189
Streptococcus agalactiae 85, 89
Streptococcus pneumoniae 45, 85, 141
 structured intermittent therapy 43
 Summer Policy Retreat (SPR) 8, 10, 189
 Summit on Development of Infectious Disease Therapeutics 68
 syphilis 68, 108-109, 114-115, 129
 systemic lupus erythematosus (SLE) i, 52-53, 69, 86, 88, 103-104, 189

T

T cell 33-35, 44, 62-63, 76, 86-87, 98, 124, 133, 135, 137
 technologies i-ii, 4, 17, 25-26, 31, 33, 35, 38, 47, 56, 61-62, 68, 70, 83-86, 111, 122, 126, 130-132, 134, 138, 140, 172-173
 Technology Evaluation Advisory Committee (TEAC) 172, 189
 technology transfer 4, 57, 122, 129, 136, 138, 172
 Terry Beirn Community Programs for Clinical Research on AIDS 12, 16, 42, 66, 107, 170, 183
 Tetramer Core Facility 137
 Tetramer Facility 95, 124, 133
 The Institute for Genomic Research 85, 121, 189
 therapeutics ii, 12, 22-24, 28, 34, 42, 44, 54, 56-58, 65-66, 70, 72, 75-76, 78, 81, 84, 91, 100, 111, 122, 136, 140
 Therapeutics Research on AIDS-Associated Opportunistic Infections and Malignancies Program 44, 65
 thyroiditis 103
 topical microbicides 11, 14, 42, 68, 106, 109-110, 114-117
 Topical Microbicides Program 109, 110, 114
Toxoplasma gondii 55, 83-84, 89
 transmissible spongiform encephalopathy (TSE) 81-82, 189
 transplantation iii, 9, 17-19, 53, 69, 87, 98-99, 104, 110, 112, 118-120, 143-145, 154
Trichomonas vaginalis 89, 109
 trimethoprim-sulfamethoxazole (TMP-SMX) 46, 189
 tropical diseases 28, 90, 170
 Tropical Diseases Research Units (TDRU) 101, 189

Tropical Medicine Research Centers (TMRC) 24, 92, 189
Trypanosoma brucei 83, 89
Trypanosoma cruzi 85, 89
 trypanosomiasis 89
 tuberculosis (TB) i-ii, 9, 22-24, 28, 42, 46-47, 55, 58, 65-66, 71-72, 74, 78, 83, 86, 89-91, 93, 111, 121, 123-126, 129, 132, 134, 138, 141-144, 164-165, 171, 173, 175, 186, 189
 Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF) 122, 144, 189
 Tuberculosis Research Unit (TBRU) 24, 46, 91, 111, 121-122, 189
 tularemia 9, 56, 73, 89
 typhoid fever 89

U

U.S. Agency for International Development (USAID) 93, 100, 121, 130, 134, 189
 U.S. Army Medical Research and Materiel Command (USAMRMC) 41, 128, 147, 189
 U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) 34, 58-59, 189
 U.S. Immunodeficiency Network (USIDNET) 20, 189
 U.S.-Japan Cooperative Medical Science Program (USJCMSP) 92, 102

V

Vaccine Action Program 102
 Vaccine and Treatment Evaluation Units 22, 46, 68, 101, 130
 vaccine candidates ii, 14, 31-36, 40, 56, 63, 80, 100-101, 111, 122, 125, 127, 129, 132, 134-135, 138, 173
 Vaccine Developmental Resources Group (VDRG) 129, 189
 Vaccine Pilot Plant (VPP) 32, 135, 190
 vaccine research and development ii, 13, 40, 126, 128, 130, 133
 vaccinia 36, 40, 51, 54-56, 58-60, 67, 127, 134, 139, 173-174, 186

vaginitis 89
 vancomycin-resistant enterococci (VRE) 45, 141, 190
 varicella-zoster virus (VZV) 67, 139, 190
Vibrio cholerae 46, 55, 84-85, 89
 viral hemorrhagic fevers 73, 139
 Virion Infectivity Factor (Vif) 39, 190
 viruses ii, 17, 21, 24, 26, 28, 30, 32-33, 56, 59, 61, 64, 67, 73-77, 80, 89, 132-133, 139
 VRC. *See* Dale and Betty Bumpers Vaccine Research Center

W

Walter Reed Army Institute of Research 101, 151, 153
 Warren Grant Magnuson Clinical Center 3, 26, 70
 Wegener's granulomatosis (WG) 70, 142, 190
 West Nile virus (WNV) i, 6, 22-23, 28, 30-31, 34, 36, 55, 59-60, 67-68, 71, 74, 76-77, 89, 129, 133, 135, 139, 173-174, 190
 Winter Program Review (WPR) 8, 10, 190
Wolbachia 89
 Women and Infants Transmission Study (WITS) 11, 16, 105, 136, 190
 women's health 38, 103
 Women's Interagency HIV Study (WIHS) 11, 16, 105-106, 136, 190
 World Health Organization (WHO) v, 74, 93, 102, 111, 121, 123, 130, 136, 139, 141, 190
 World Reference Center for Arboviruses 77

X

xenotransplantation 120

Y

yellow fever 77, 89, 139
Yersinia pestis 55, 58, 73, 84-85, 89

GENERAL INFORMATION

DIRECTORY OF NIAID PERSONNEL^a

	Bldg. ^b	Room	Phone	E-mail
OFFICE OF THE DIRECTOR (OD)				
Anthony S. Fauci, M.D., <i>Director</i>	31	7A03	(301) 496-2263	af10r@nih.gov
H. Clifford Lane, M.D., <i>Acting Deputy Director</i>	10	11S231	(301) 496-7196	cl17d@nih.gov
Mark Dybul, M.D., <i>Assistant Director for Medical Affairs</i>	31	7A03	(301) 496-2263	md129j@nih.gov
Gregory K. Folkers, <i>Senior Public Affairs Advisor</i>	31	7A03	(301) 496-2263	gfolkers@nih.gov
Robin Gruber, <i>Special Assistant to the Director</i>	31	7A03	(301) 496-9118	rogruber@mail.nih.gov
Hillary Harvey, Ph.D., <i>Special Assistant to the Director</i>	31	7A03	(301) 496-9118	hharvey@niaid.nih.gov
Carole Hudgings, Ph.D., <i>Senior Advisor to the Deputy Director</i>	31	7A03	(301) 496-9118	chudgings@nih.gov
Margaret A. Moore, <i>Chief of Staff</i>	31	7A03	(301) 496-9118	mm52s@nih.gov
Ernie Takafuji, M.D., MPH, <i>Assistant Director for Biodefense Research</i>	6610	5111	(301) 451-1462	etakafuji@niaid.nih.gov
Nancy Touchette, Ph.D., <i>Special Assistant to the Director</i>	31	7A03	(301) 496-9118	ntouchette@niaid.nih.gov
Karl A. Western, M.D., D.T.P.H., <i>Assistant Director for International Research</i>	6610	2200	(301) 496-6721	kw@niaid.nih.gov
OFFICE OF BIODEFENSE RESEARCH				
Ernie Takafuji, M.D., MPH, <i>Assistant Director for Biodefense Research</i>	6610	5111	(301) 451-1462	etakafuji@niaid.nih.gov
OFFICE OF CLINICAL RESEARCH (OCR)				
H. Clifford Lane, M.D., <i>Director</i>	10	11S231	(301) 496-7196	cl17d@nih.gov
OFFICE OF GLOBAL AFFAIRS (OGA)				
Karl A. Western, M.D., D.T.P.H., <i>Director</i>	6610	2200	(301) 496-6721	kw@niaid.nih.gov
ASSOCIATE DIRECTOR FOR MANAGEMENT AND OPERATIONS (ADMO)				
Lynn C. Hellinger, <i>Associate Director for Management and Operations</i>	31	7A16	(301) 594-3964	lh28q@nih.gov
Office of Administrative Services (OAS)				
Susan Cook, <i>Acting Director</i>	31	7A19	(301) 496-1521	sc67r@nih.gov
Acquisition Management and Operations Branch (AMOB)				
Rebecca A. Guenther, <i>Chief</i>	6700B	1131	(301) 402-2284	rg45t@nih.gov
Extramural Administrative Management Branch (EAMB)				
Marilyn E. Kunzweiler, <i>Chief</i>	6700B	1140	(301) 496-7151	mk34g@nih.gov
Intramural Administrative Management Branch (IAMB)				
Katy Perry, <i>Acting Chief</i>	10	4A26	(301) 496-7089	kperry@niaid.nih.gov
Management Services Branch (MSB)				
Susan Cook, <i>Chief</i>	31	7A19	(301) 496-1521	sc67r@nih.gov
Office of Communications and Public Liaison (OCPL)				
Laurie Doepel, <i>Acting Director</i>	31	7A50	(301) 496-5717	ldoepel@mail.nih.gov
Office of Ethics (OE)				
Art Bennett, <i>Director</i>	6610	4019	(301) 435-6542	bennettar@niaid.nih.gov
Office of Financial Management (OFM)				
Ralph Tate, <i>Director</i>	31	7A08	(301) 496-4701	rtate@niaid.nih.gov
Office of Human Resources Management (OHRM)				
Charlene Watson, <i>Chief</i>	31	7A20	(301) 496-9686	chwatson@niaid.nih.gov
Office of Management for New Initiatives (OMNI)				
Julie Brown, <i>Acting Director</i>	6610	2043	(301) 451-4328	jbrown@niaid.nih.gov

	Bldg. ^b	Room	Phone	E-mail
Office of Policy Analysis (OPA)				
Karin Lohman, Ph.D., <i>Acting Director</i>	31	7A16	(301) 594-3964	klohman@niaid.nih.gov
Office of Technology Development (OTD)				
Michael Mowatt, Ph.D., <i>Director</i>	31	3B62	(301) 496-2644	mm25q@nih.gov
Office of Technology Information Systems (OTIS)				
Michael Tartakovsky, <i>Director</i> <i>Chief Information Officer</i>	31	7A32	(301) 496-8219	mtartakovs@mail.nih.gov
Extramural Network Systems Branch (ENSB)				
Kim L. Kassing, <i>Chief</i>	6700B	4124	(301) 402-3580	kk15w@nih.gov
Intramural Technical Systems Branch (ITSB)				
Jonathan Folkers, <i>Acting Chief</i>	10	4A30A	(301) 496-0205	jfolkers@mail.nih.gov
Management Information Systems Branch (MISB)				
Brian Connelley, <i>Acting Chief</i>	40	1504B	(301) 435-3675	bconnellev@mail.nih.gov
DALE AND BETTY BUMPERS VACCINE RESEARCH CENTER (VRC)				
Gary J. Nabel, M.D., Ph.D., <i>Director</i>	40	4502	(301) 496-1852	gn34v@nih.gov
John Mascola, M.D., <i>Deputy Director</i>	40	5512	(301) 594-8490	jm557m@nih.gov
Abe Mittelman, <i>Associate Director for</i> <i>Management and Operations</i>	40	1120	(301) 594-8493	amittelm@mail.nih.gov
Laboratory of Animal Medicine (LAM)				
Srinivas S. Rao, Ph.D., D.V.M., <i>Chief</i>	40	1407	(301) 594-8465	srao1@mail.nih.gov
Laboratory of Clinical Trials (LCT)				
Barney S. Graham, M.D., Ph.D., <i>Chief</i>	40	2502	(301) 594-8468	bg118j@nih.gov
Laboratory of Core BSL-3 Virology				
John Mascola, M.D., <i>Deputy Director</i>	40	5512	(301) 496-1852	jmascola@nih.gov
Laboratory of Core Flow Cytometry				
Mario Roederer, Ph.D., <i>Chief</i> , <i>ImmunoTechnology Section</i>	40	5509	(301) 594-8491	roederer@nih.gov
Laboratory of Core Immunology				
Robert Bailer, Ph.D., <i>Manager</i>	40	3510	(301) 594-8481	rbailer@mail.nih.gov
Laboratory of Core Vector				
Gary J. Nabel, M.D., Ph.D., <i>Director</i>	40	4502	(301) 594-1852	gnabel@nih.gov
Laboratory of Immunology (LI)				
Richard Koup, M.D., <i>Chief</i>	40	3502	(301) 594-8585	rk173f@nih.gov
Laboratory of Structural Virology				
Richard Wyatt, Ph.D., <i>Chief</i>	40	4512	(301) 594-8690	richw@mail.nih.gov
Laboratory of Vaccine Production (LVP)				
Phillip Gomez III, Ph.D., <i>Chief</i>	40	5502	(301) 594-8485	pgomez@nih.gov
Laboratory of Viral Pathogenesis (LVP)				
Barney S. Graham, M.D., <i>Chief</i>	40	2502	(301) 594-8468	bg118j@nih.gov
Laboratory of Virology (LV)				
Gary J. Nabel, M.D., Ph.D., <i>Chief</i>	40	4502	(301) 496-1852	gn34v@nih.gov
Laboratory of Advanced Clinical Development (LACD)				
John G. McNeil, M.D., M.P.H., <i>Chief</i>	40	2512	(301) 451-8553	jomcneil@mail.nih.gov
DIVISION OF ACQUIRED IMMUNODEFICIENCY SYNDROME (DAIDS)				
Edmund C. Tramont, M.D., <i>Director</i>	6700B	4142	(301) 496-0545	et89f@nih.gov
Jonathan M. Kagan, Ph.D., <i>Deputy Director</i>	6700B	4140	(301) 496-0545	jk38m@nih.gov
Basic Sciences Program (BSP)				
Carl W. Dieffenbach, Ph.D., <i>Director</i>	6700B	4101	(301) 496-0637	cd17u@nih.gov

	Bldg. ^b	Room	Phone	E-mail
Clinical Research Management Branch (CRMB)				
Margaret Matula, R.N., <i>Chief</i>	6700B	5115	(301) 496-8214	mm154j@nih.gov
Clinical Research Resources Branch (CRRB)				
Pamela Scanlan, M.A., <i>Chief</i>	6700B	4117	(301) 496-0701	ps27s@nih.gov
Drug Development and Clinical Sciences Branch (DDCSB)				
Michael Ussery, Ph.D., <i>Chief</i>	6700B	5150	(301) 496-0636	mu15s@nih.gov
Epidemiology Branch (EB)				
Carolyn Williams, Ph.D., <i>Chief</i>	6700B	4102	(301) 402-0135	cw237k@nih.gov
HIV Research Branch (HIVRB)				
Carla B. Pettinelli, M.D., Ph.D., <i>Chief</i>	6700B	5102	(301) 496-0700	cp22n@nih.gov
DAIDS International Research Branch (DIRB)				
Rod Hoff, Ph.D., <i>Director</i>	6700B	4148	(301) 496-6179	rh25v@nih.gov
Office for Policy in Clinical Research Operations (OPCRO)				
Richard Hafner, M.D., <i>Director</i>	6700B	4116	(301) 451-2734	rhafner@niaid.nih.gov
Office of Program Operations and Scientific Information (OPOSI)				
Matthew Murguia, <i>Director</i>	6700B	4140	(301) 496-0545	mm768e@nih.gov
Complications and Co-Infections Research Branch (CCRB)				
Barbara E. Laughon, Ph.D., <i>Chief</i>	6700B	5108	(301) 402-2304	bl17u@nih.gov
Pathogenesis and Basic Research Branch (PBRB)				
Susan F. Plaeger, Ph.D., <i>Chief</i>	6700B	4149	(301) 496-8378	sp218p@nih.gov
Pediatric Medicine Branch (PMB)				
Vacant, <i>Chief</i>	6700B	5154	(301) 402-2300	
Pharmaceutical Affairs Branch (PAB)				
Ana I. Martinez, Ph.D., <i>Chief</i>	6700B	4115	(301) 496-8213	am30c@nih.gov
Preclinical Research and Development Branch (PRDB)				
James Bradac, Ph.D., <i>Chief</i>	6700B	5116	(301) 402-0121	jb68k@nih.gov
Prevention Sciences Branch (PSB)				
Kevin Ryan, Ph.D., <i>Chief</i>	6700B	5134	(301) 496-6177	kr90p@nih.gov
Regulatory Affairs Branch (RAB)				
MaryAnne Luzar, Ph.D., <i>Chief</i>	6700B	4114	(301) 435-3741	ml29g@nih.gov
Targeted Interventions Branch (TIB)				
Sandra Bridges, Ph.D., <i>Chief</i>	6700B	4154	(301) 496-8197	sb33j@nih.gov
Therapeutics Research Program (TRP)				
Sandra Lehrman, M.D., <i>Director</i>	6700B	5101	(301) 496-8210	sl356i@nih.gov
Vaccine and Prevention Research Program (VPRP)				
Margaret I. Johnston, Ph.D., <i>Director</i>	6700B	5142	(301) 402-0846	pj7p@nih.gov
Vaccine Clinical Research Branch (VCRB)				
Jorge E. Flores, M.D., <i>Chief</i>	6700B	5133	(301) 496-8200	jf30t@nih.gov
DIVISION OF ALLERGY, IMMUNOLOGY AND TRANSPLANTATION (DAIT)				
Daniel Rotrosen, M.D., <i>Director</i>	6610	3111	(301) 496-1886	dr17g@nih.gov
Vacant, <i>Deputy Director</i>	6610	3109	(301) 496-1886	
Office of Clinical Applications (OCA)				
Daniel Rotrosen, M.D., <i>Acting Director</i>	6610	3109	(301) 496-1886	dr17g@nih.gov
Office of Epidemiology and Clinical Trials (OECT)				
Capt. Ernestine T. Smartt, R.N., <i>Director</i>	6610	3069	(301) 496-7353	es23r@nih.gov
Office of Program Planning, Operations, and Scientific Information (OPOSI)				
Jean McKay, <i>Director</i>	6610	3119	(301) 496-1886	jmckay@niaid.nih.gov
Carole Cole, <i>Deputy Director</i>	6610	3120	(301) 496-1886	ccole@niaid.nih.gov

	Bldg. ^b	Room	Phone	E-mail
Asthma, Allergy, and Inflammation Branch (AAIB)				
Chuck Hackett, Ph.D., <i>Chief</i>	6610	3103	(301) 496-8973	chackett@nih.gov
Basic Immunology Branch (BIB)				
Helen R. Quill, Ph.D., <i>Chief</i>	6610	3013	(301) 496-7551	hq1t@nih.gov
Clinical Immunology Branch (CIB)				
Vacant, <i>Chief</i>	6610	3019	(301) 496-7104	
Transplantation Immunobiology Branch (TIB)				
Shiv Prasad, Ph.D., <i>Chief</i>	6610	3035	(301) 496-5598	spasad@niaid.nih.gov
DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID)				
Carole A. Heilman, Ph.D., <i>Director</i>	6610	6111	(301) 496-1884	ch25v@nih.gov
Pamela M. McInnes, D.D.S., <i>Deputy Director</i>	6610	6113	(301) 496-1884	pm23m@nih.gov
Office of Biodefense Research Activities				
Deborah Katz, M.S., R.N., <i>Acting Director</i>	6610	5111	(301) 402-8539	dk30f@nih.gov
Office of Clinical Research Affairs (OCRA)				
Holli Hamilton, M.D., M.P.H., <i>Director</i>	6610	6045	(301) 496-7067	hh88f@nih.gov
Office of Regulatory Affairs (ORA)				
Lydia Falk, Ph.D., <i>Director</i>	6610	6035	(301) 435-2875	lf116u@nih.gov
Office of Scientific Coordination and Program Operations (OSCP0)				
Irene Glowinski, Ph.D., <i>Chief</i>	6610	6071	(301) 496-1884	ig2v@nih.gov
Bacteriology and Mycology Branch (BMB)				
Dennis M. Dixon, Ph.D., <i>Chief</i>	6610	4111	(301) 496-7728	dd24a@nih.gov
Enteric and Hepatic Diseases Branch (EHDB)				
Leslye D. Johnson, Ph.D., <i>Chief</i>	6610	4015	(301) 496-7051	lj7m@nih.gov
Parasitology and International Programs Branch (PIPB)				
Lee Hall, M.D., Ph.D., <i>Acting Chief</i>	6610	5103	(301) 496-2544	bh24q@nih.gov
Respiratory Diseases Branch (RDB)				
George Curlin, M.D., M.P.H., <i>Acting Chief</i>	6610	6119	(301) 496-5893	gc24a@nih.gov
Sexually Transmitted Infections Branch (STIB)				
Carolyn Deal, Ph.D., <i>Chief</i>	6610	5039	(301) 492-0443	cd128z@nih.gov
Virology Branch (VB)				
Catherine A. Laughlin, Ph.D., <i>Chief</i>	6610	4099	(301) 496-7453	cl28r@nih.gov
DIVISION OF EXTRAMURAL ACTIVITIES (DEA)				
John J. McGowan, Ph.D., <i>Director</i>	6700B	2142	(301) 496-7291	jm80c@nih.gov
Allan W. Czarra, <i>Deputy Director</i>	6700B	2140	(301) 496-7291	ac20a@nih.gov
Kathy Grady, <i>Special Assistant to the Director</i>	6700B	2141	(301) 496-7291	kgrady@niaid.nih.gov
Mary Nuss, <i>Committee Management Officer</i>	6700B	2147	(301) 496-7601	mnuss@mail.nih.gov
Gregory Milman, Ph.D., <i>Director, Office of Innovation and Special Programs, SBIR Programs and Division Operations</i>	6700B	2140	(301) 496-7291	gm162@nih.gov
Office of Initiative Development, Data Quality, and Integrity				
Nancy Blustein, <i>Chief</i>	6700B	2139	(301) 534-7198	nblustein@nih.gov
Office of International Extramural Activities				
Paula Strickland, Ph.D., <i>Chief</i>	6700B	2154	(301) 435-8563	pstrickland@nih.gov
Office of Knowledge Resources				
Maya Hadar, <i>Director</i>	6700B	2149	(301) 496 3773	mhadar@niaid.nih.gov
Office of Program Coordination and Operations (OPCO)				
Theresa Shrader, <i>Director</i>	6700B	2144	(301) 496-7291	tshrader@nih.gov

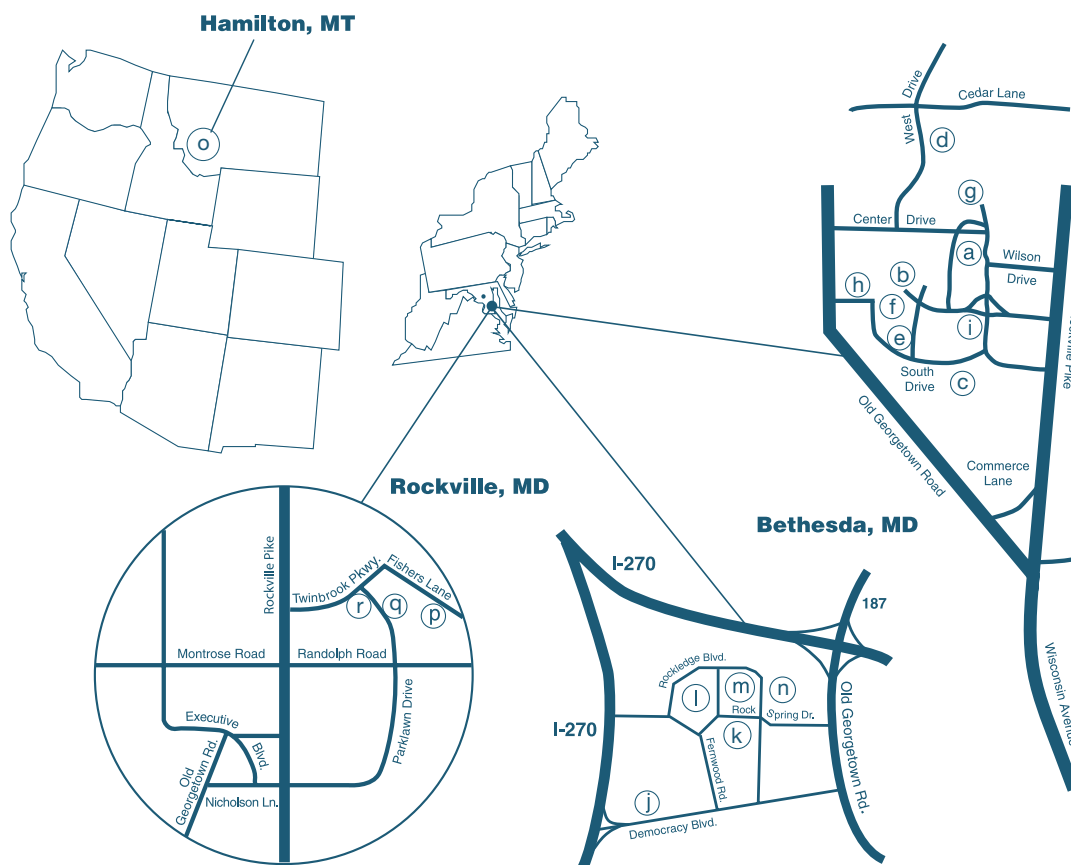
	Bldg. ^b	Room	Phone	E-mail
Office of Special Populations and Research Training (OSPRT)				
Milton J. Hernandez, Ph.D., <i>Director</i>	6700B	2133	(301) 496-8697	mh35c@nih.gov
Contract Management Program				
Chuck Grewe, <i>Chief</i>	6700B	2115	(301) 496-0612	cgrewe@nih.gov
Grants Management Branch (GMB)				
Mary C. Kirker, <i>Chief</i>	6700B	2116	(301) 496-7075	mk35h@nih.gov
Referral and Program Analysis Branch (RPAB)				
Lai S. Tan, <i>Chief</i>	6700B	2134	(301) 496-5318	lt7r@nih.gov
Scientific Review Program (SRP)				
Hortencia M. Hornbeak, Ph.D., <i>Director</i>	6700B	2101	(301) 496-2550	hh7q@nih.gov
AIDS Clinical and Epidemiology Research Review Branch (ACERRB)				
Peter R. Jackson, Ph.D., <i>Chief</i>	6700B	2154	(301) 496-2550	pj8v@nih.gov
AIDS Preclinical Research Review Branch (APRRB)				
Vacant, <i>Chief</i>	6700B	2148	(301) 496-2550	
Microbiology and Immunology Review Branch (MIRB)				
Edward Schroder, Ph.D., <i>Chief</i>	6700B	2156	(301) 496-2550	es170m@nih.gov
Special Review Branch (SRB)				
Madelon C. Halula, Ph.D., <i>Chief</i>	6700B	2150	(301) 496-2550	mh30x@nih.gov
DIVISION OF INTRAMURAL RESEARCH (DIR)				
Thomas J. Kindt, Ph.D., <i>Director</i>	10	4A31	(301) 496-9250	tk9c@nih.gov
Karyl S. Barron, M.D., <i>Deputy Director for Science Operations</i>	10	4A30	(301) 402-2208	kb18p@nih.gov
Kathryn C. Zoon, Ph.D., <i>Deputy Director for Planning and Development</i>	10	4A30	(301) 402-5469	kzoon@niaid.nih.gov
W. Randy Elkins, D.V.M., <i>Associate Director for Nonhuman Primate Research</i>	TWNII	201D	(301) 496-0560	re9k@nih.gov
Wendy J. Fibison, Ph.D., <i>Associate Director for Training and Special Emphasis Programs</i>	15B-1	103	(301) 496-6400	wf15c@nih.gov
Robert Hohman, Ph.D., <i>Associate Director for Development of Research Technologies</i>	TWNI	1004	(301) 594-8198	rh13q@nih.gov
Comparative Medicine Branch (CMB)				
W. Randy Elkins, D.V.M., <i>Acting Chief</i>	TWNII	201D	(301) 496-0560	re9k@nih.gov
Infectious Disease Pathogenesis Branch (IDPB)				
W. Randy Elkins, D.V.M., <i>Chief</i>	TWNII	201D	(301) 496-0560	re9k@nih.gov
Laboratory of Allergic Diseases (LAD)				
Dean D. Metcalfe, M.D., <i>Chief</i>	10	11C205	(301) 496-1267	dm15o@nih.gov
Laboratory of Cellular and Molecular Immunology (LCMI)				
Ronald H. Schwartz, M.D., Ph.D., <i>Chief</i>	4	111	(301) 496-8108	rs34r@nih.gov
Laboratory of Clinical Infectious Diseases (LCID)				
Steven M. Holland, M.D., <i>Chief</i>	10	11N103	(301) 402-7684	sholland@niaid.nih.gov
Laboratory of Host Defenses (LHD)				
Harry L. Malech, M.D., <i>Chief</i>	10	11N113	(301) 496-1343	hm5s@nih.gov
Laboratory of Human Bacterial Pathogenesis (LHBP)				
Thomas G. Schwan, Ph.D., <i>Acting Chief</i>	RML		(406) 363-9250	tschwan@niaid.nih.gov
Laboratory of Immunogenetics (LIG)				
Susan K. Pierce, Ph.D., <i>Chief</i>	TWNII	200B	(301) 496-9589	sp217q@nih.gov
Laboratory of Immunology (LI)				
William E. Paul, M.D., <i>Chief</i>	10	11N311	(301) 496-5046	wp1k@nih.gov
Ronald N. Germain, M.D., Ph.D., <i>Deputy Chief</i>	10	11D14	(301) 496-1904	rg14b@nih.gov

	Bldg. ^b	Room	Phone	E-mail
Laboratory of Immunopathology (LIP)				
Herbert C. Morse III, M.D., <i>Chief</i>	7	304	(301) 496-6379	hm16c@nih.gov
Laboratory of Immunoregulation (LIR)				
Anthony S. Fauci, M.D., <i>Chief</i>	10	11B13	(301) 496-1124	af10r@nih.gov
Laboratory of Infectious Diseases (LID)				
Brian R. Murphy, M.D., <i>Co-Chief</i>	7	106	(301) 496-4205	bm25f@nih.gov
Robert Purcell, M.D., <i>Co-Chief</i>	7	202	(301) 496-6227	rp18p@nih.gov
Laboratory of Intracellular Parasites (LICP)				
Harlan D. Caldwell, Ph.D., <i>Chief</i>	RML		(406) 363-9333	hcaldwell@niaid.nih.gov
Laboratory of Malaria and Vector Research (LMVR)				
Thomas E. Welles, M.D., Ph.D., <i>Acting Chief</i>	4	126	(301) 402-1274	tw4i@nih.gov
Laboratory of Molecular Immunology (LMI)				
Philip M. Murphy, M.D., <i>Acting Chief</i>	10	11N112	(301) 496-2877	pmurphy@niaid.nih.gov
Laboratory of Molecular Microbiology (LMM)				
Malcolm A. Martin, M.D., <i>Chief</i>	4	315	(301) 496-4012	mm54y@nih.gov
Laboratory of Parasitic Diseases (LPD)				
F. Alan Sher, Ph.D., <i>Acting Chief</i>	4	126	(301) 496-1274	as28c@nih.gov
Laboratory of Persistent Viral Diseases (LPVD)				
Bruce W. Chesebro, M.D., <i>Chief</i>	RML		(406) 363-9354	bchesebro@nih.gov
Laboratory of Viral Diseases (LVD)				
Bernard Moss, M.D., Ph.D., <i>Chief</i>	4	229A	(301) 496-9421	bm26f@nih.gov
Malaria Vaccine Development Branch (MVDB)				
Louis H. Miller, M.D., <i>Co-Chief</i>	TWNI	1113	(301) 435-2177	lmiller@niaid.nih.gov
Allan Saul, Ph.D., <i>Co-Chief</i>	TWNI	1111	(301) 594-2701	asaul@niaid.nih.gov
Molecular and Cellular Immunogenics Section				
Thomas J. Kindt, Ph.D., <i>Director</i>	10	4A31	(301) 496-9250	tk9c@nih.gov
Research Technologies Branch (RTB)				
Robert Hohman, Ph.D., <i>Chief</i>	TWNI	1004	(301) 495-8198	rh13q@nih.gov
Rocky Mountain Veterinary Branch (RMVB)				
Michael J. Parnell, D.V.M., Ph.D., <i>Chief</i>	RML		(406) 363-9238	mp24s@nih.gov

^a Current as of December 31, 2004. For locating personnel not listed, the telephone number for general NIH information is (301) 496-4000. Information is available online at www.niaid.nih.gov/cgi-sb/contacts/contacts.cfm. For direct dialing, the area code is 301, unless otherwise noted.

^b 6610 —6610 Rockledge Drive, Rockville, MD 20892
6700B —6700B Rockledge Drive, Bethesda, MD 20892
Democracy 2 —Office of Management for New Initiatives, 6707 Democracy Boulevard, Suite 880, Bethesda, MD 20892
FCRDC —Frederick Cancer Research and Development Center, Building 550, Fort Detrick, MD 21702
RML —Rocky Mountain Laboratories, 903 South Fourth Street, Hamilton, MT 59840-2999
TWN1 —Twinbrook I Building, 5640 Fishers Lane, Rockville, MD 20852
TWNII —Twinbrook II Building, 12441 Parklawn Drive, Rockville, MD 20852
Building 4 —NIH Campus, 9000 Rockville Pike, Bethesda, MD 20892
Building 7 —NIH Campus, 9000 Rockville Pike, Bethesda, MD 20892
Building 10 —NIH Campus, 9000 Rockville Pike, Bethesda, MD 20892
Building 14B-S —NIH Campus, 9000 Rockville Pike, Bethesda, MD 20892
Building 15B-1 —NIH Campus, 9000 Rockville Pike, Bethesda, MD 20892
Building 31 —NIH Campus, 9000 Rockville Pike, Bethesda, MD 20892
Building 40/VRC —Dale and Betty Bumpers Vaccine Research Center, NIH Campus, 9000 Rockville Pike, Bethesda, MD 20892
Building 50 —NIH Campus, 9000 Rockville Pike, Bethesda, MD 20892

LOCATION OF BUILDINGS OCCUPIED BY NIAID PERSONNEL



- | | | |
|--|---|---|
| <p>a Building 4
NIH Campus
9000 Rockville Pike
Bethesda, MD 20892</p> <p>b Building 10
NIH Campus
9000 Rockville Pike
Bethesda, MD 20892</p> <p>c Building 14B-S
NIH Campus
9000 Rockville Pike
Bethesda, MD 20892</p> <p>d Building 15B-1
NIH Campus
9000 Rockville Pike
Bethesda, MD 20892</p> <p>e Building 29
NIH Campus
9000 Rockville Pike
Bethesda, MD 20892</p> <p>f Building 30
NIH Campus
9000 Rockville Pike
Bethesda, MD 20892</p> | <p>g Building 31
NIH Campus
9000 Rockville Pike
Bethesda, MD 20892</p> <p>h Building 40/VRC
NIH Campus
9000 Rockville Pike
Bethesda, MD 20892</p> <p>i Building 50
NIH Campus
9000 Rockville Pike
Bethesda, MD 20892</p> <p>j Democracy 2
6707 Democracy Boulevard
Suite 880
Bethesda, MD 20892</p> <p>k Fernwood Building
10401 Fernwood Road
Bethesda, MD 20892</p> <p>l Rockledge Building (6700A)
6700 A Rockledge Drive
Bethesda, MD 20892</p> | <p>m Rockledge Building (6700B)
6700 B Rockledge Drive
Bethesda, MD 20892</p> <p>n Rockledge Building (6610)
6610 Rockledge Drive
Bethesda, MD 20892</p> <p>o Rocky Mountain Laboratories
903 South Fourth Street
Hamilton, MT 59840</p> <p>p Twinbrook Building #1
5640 Fishers Lane
Rockville, MD 20857</p> <p>q Twinbrook Building #2
12441 Parklawn Drive
Rockville, MD 20857</p> <p>r Twinbrook Building #3
12735 Parklawn Drive
Rockville, MD 20857</p> |
|--|---|---|

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health



National Institute of Allergy and Infectious Diseases

NIH Publication No. 04-7370

April 2005

www.niaid.nih.gov